S. Report

L3 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
AB The present invention relates to novel protein variants that exhibit reduced allergenicity when compared to the parental proteins. Also included are DNA mols. that encode the novel variants, host cells comprising the DNA and methods of making proteins less allergenic. The protein variants are e.g. Bacillus amyloliquefaciens subtilisin protease and its substitution, deletion or addn. mutants having altered T cell epitope. The subtilisin and variants are useful in compns. including pharmaceutical, laundry, cosmetic, dish, hard surface, skin care, hair care, beauty care, oral care and **contact lens**.
IT 50-81-7, Vitamin C, biological studies 56-81-5, Glycerol, biological studies 57-55-6, Propylene glycol, biological studies 58-95-7, Vitamin E acetate 64-17-5, Ethanol, biological studies 68-26-8, Retinol 69-72-7, Salicylic acid, biological studies 79-81-2, Retinyl palmitate 79-83-4, Vitamin B3 **81-13-0**, Panthenol 83-67-0, Theobromine 98-92-0, Niacinamide 302-79-4, Retinoic acid 1406-18-4, Vitamin E 4602-84-0, Farnesol 7069-42-3, Retinyl propionate 7732-18-5, Water, biological studies 25265-75-2, Butylene glycol 25322-68-3, Polyethylene glycol 25322-69-4, Polypropylene glycol 62309-51-7, Propanol 74563-64-7, Phytantriol 214047-00-4
RL: BUU (Biological use, unclassified); COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(subtilisin protease and variants with reduced allergenicity for use in pharmaceutical, cleaning and cosmetic products)

L3 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
AB This invention relates to ophthalmic solns. for **contact lens** users and for treating dry eye symptoms. The solns. comprise (1) panthenol, (2) boric acid and/or salts thereof, and (3) compds. which contain .gtoreq. 3 OH groups, such as glycerin, mannitol, glucose, and .alpha.-cyclodextrin. The solns. provide excellent bactericidal activities without irritation. An eyedrop soln. contained panthenol 0.05, boric acid 1, mannitol 1, NaHCO3 0.05, NaCl 0.5, benzalkonium chlorides 0.003, NaOH or HCl q.s. to pH 5, and distd. water balance to 100 %.
ST ophthalmic soln panthenol borate dry eye; **contact lens** eyedrop panthenol borate mannitol
IT 50-99-7, D-Glucose, biological studies 56-81-5, Glycerin, biological studies 58-56-0, Pyridoxine hydrochloride 60-32-2, .epsilon.-Aminocaproic acid 69-65-8, D-Mannitol **81-13-0**, Panthenol 113-92-8, Chlorpheniramine maleate 522-48-5, Tetrahydrozoline hydrochloride 550-99-2, Naphazoline hydrochloride 10016-20-3, .alpha.-Cyclodextrin 10043-35-3, Boric acid, biological studies 68797-35-3, Dipotassium glycyrrhizinate
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ophthalmic solns. contg. stabilized panthenol)

L3 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AB The invention provides a procedure for the manuf. of contact lenses for eye treatment, eye protection and eye-care wherein the lenses are impregnated with a suitable compn. The invention also provides a compn. for the impregnation of a **contact lens** for the treatment and/or care and/or protection of the eye, a kit contg. such a compn. and one or more contact lenses. Thus, a formulation contained PHMB-2HCl 2.5 ppm, boric acid 0.75, borax 0.15, NaCl 0.40, EDTA sodium 0.03, HPMC 0.10, and dexpanthenol 1.0%.
ST eye **contact lens** soln
IT 50-14-6, Calciferol 50-81-7, Ascorbic acid, biological studies 57-50-1, Saccharose, biological studies 58-85-5, Biotin 59-43-8, Thiamine, biological studies 59-67-6, Nicotinic acid, biological studies 65-23-6, Pyridoxine 68-26-8, Retinol 68-26-8D, Retinol, derivs. 79-83-4, Pantothenic acid **81-13-0**, Dexpanthenol 83-88-5, Riboflavin, biological studies 98-92-0, Nicotinic amide 104-32-5D, Propamidine, derivs. 107-35-7, Taurine 127-17-3D, Pyruvic acid,

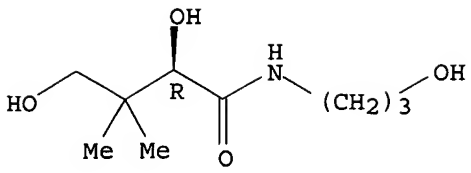
derivs. 305-84-0, Carnosine 328-50-7, .alpha.-Ketoglutaric acid 1406-16-2, Vitamin D 1406-16-2D, Vitamin D, derivs. 7440-66-6, Zinc, biological studies 7440-70-2, Calcium, biological studies 7782-49-2, Selenium, biological studies 9001-05-2, Catalase 9004-61-9, Hyaluronic acid 9004-61-9D, Hyaluronic acid, salts 9005-49-6, Heparin, biological studies 12001-79-5, Vitamin K 16110-51-3, Cromoglycic acid 37259-58-8, Serine protease 58581-89-8, Azelastine 62031-54-3, FGF 62229-50-9, EGF 69049-73-6, Nedocromil
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compn. for treatment and/or care of eye)

L3 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
TI **Contact lens** care solutions containing dexpanthenol
AB The present invention relates to **contact lens** care product comprising dexpanthenol. The invention similarly relates to the usage of a **contact lens** care compns. for cleaning and optionally disinfecting contact lenses. Thus, a formulation contained dexpanthenol 10.0, EDTA 1.0, NaCl 7.0, Tris buffer 2.5, and PHMB 0.001 g/L, and water to 1000 mL.
ST **contact lens** soln dexpanthenol
IT Buffers
Complexing agents
Contact lenses
Disinfectants
Surfactants
(**contact lens** care solns. contg. dexpanthenol)
IT Contact lenses
(hard; **contact lens** care solns. contg. dexpanthenol)
IT Antimicrobial agents
Viscosity
(modifiers; **contact lens** care solns. contg. dexpanthenol)
IT 50-70-4, D-Sorbitol, biological studies 60-00-4, EDTA, biological studies **81-13-0**, Dexpanthenol 126-72-7, Tris 1330-43-4, Sodium borate 7447-40-7, Potassium chloride (KCl), biological studies 7558-79-4, Disodium hydrogen phosphate 7558-80-7, Sodium dihydrogen phosphate 7632-04-4, Sodium perborate 7647-14-5, Sodium chloride, biological studies 9004-62-0, Hydroxyethyl cellulose 9004-65-3, Methocel E5 10043-35-3, Boric acid, biological studies 32289-58-0 106392-12-5, Pluronic
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**contact lens** care solns. contg. dexpanthenol)

L3 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
ST silicone rubber **contact lens**
IT **81-13-0**, Pantothenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(polymn. of, with diisocyanates and hydroxy-terminated tetramethyldisiloxane)

L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2003 ACS
RN 81-13-0 REGISTRY
CN Butanamide, 2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethyl-, (2R)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Butanamide, 2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethyl-, (R)-
CN Butyramide, 2,4-dihydroxy-N-(3-hydroxypropyl)-3,3-dimethyl-, D-(+)- (8CI)
OTHER NAMES:
CN Alcopan 250
CN Bepanthen
CN Bepanthene
CN Bepantol
CN Cozyme
CN D(+)-.alpha.,.gamma.-Dihydroxy-N-(3-hydroxypropyl)-.beta.,.beta.-dimethylbutyramide
CN D(+)-2,4-Dihydroxy-N-(3-hydroxypropyl)-3,3-dimethylbutyramide
CN D(+)-Panthenol
CN D(+)-Pantothenyl alcohol
CN D-P-A Injection
CN d-Panthenol
CN D-Panthenol
CN d-Panthenol 50
CN d-Pantothenol
CN D-Pantothenyl alcohol
CN d-Pantothenyl alcohol
CN **Dexpanthenol**
CN Ilopan
CN Intrapan
CN Motilyn
CN Panadon
CN Pantenyl
CN Panthenol
CN Panthenol, (+)-
CN Panthoderm
CN Pantol
CN Pantothenol
CN Pantothenyl alcohol
CN Propanolamine, N-pantoyl-
CN Provitamin B
CN Provitamin B5
CN Synapan
CN Thenalton
CN Urupan
CN Zentinic
FS STEREOSEARCH
DR 1113-70-8, 17307-32-3
MF C9 H19 N O4
CI COM
LC STN Files: ADISNEWS, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAOLD, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CHEMINFORMRX, CHEMLIST, CIN, CSCHEM, DDFU, DIOGENES, DRUGU, EMBASE, HODOC*, HSDB*, IFICDB, IFIPAT, IFIUDB, IPA, MEDLINE, MRCK*, MSDS-OHS, NAPRALERT, PHARMASEARCH, PIRA, PROMT, RTECS*, TOXCENTER, USAN, USPAT2, USPATFULL
(*File contains numerically searchable property data)
Other Sources: DSL**, EINECS**, TSCA**, WHO
(**Enter CHEMLIST File for up-to-date regulatory information)

Absolute stereochemistry.




**PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT**

826 REFERENCES IN FILE CA (1962 TO DATE)
25 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
829 REFERENCES IN FILE CAPLUS (1962 TO DATE)
19 REFERENCES IN FILE CAOLD (PRIOR TO 1967)

Parent

L3 ANSWER 1 OF 7 USPATFULL
AN 2002:280517 USPATFULL
TI Lens care product containing dexpanthenol
IN Schwind, Peter, Hosbach-Rottenberg, GERMANY, FEDERAL REPUBLIC OF
Scherer, Anton, Frammersbach, GERMANY, FEDERAL REPUBLIC OF
PI US 2002155961 A1 20021024
AI US 2002-44373 A1 20020111 (10)
PRAI EP 2001-100764 20010112
CH 2001-1035 20010607
DT Utility
FS APPLICATION
LN.CNT 385
INCL INCLM: 510/112.000
NCL NCLM: 510/112.000
IC [7]
ICM: C11D001-00
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 2 OF 7 USPATFULL
AN 97:12160 USPATFULL
TI Mascara composition
IN Mausner, Jack, New York, NY, United States
PA Chanel, Inc., Piscataway, NJ, United States (U.S. corporation)
PI US 5601810 19970211
AI US 1995-561516 19951122 (8)
DT Utility
FS Granted
LN.CNT 641
INCL INCLM: 424/070.700
NCL NCLM: 424/070.700
IC [6]
ICM: A61K007-032
EXF 424/70.7
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 3 OF 7 USPATFULL
AN 95:94676 USPATFULL
TI Mascara composition
IN Mausner, Jack, New York, NY, United States
PA Chanel, Inc., New York, NY, United States (U.S. corporation)
PI US 5460808 19951024
AI US 1994-192192 19940204 (8)
RLI Continuation of Ser. No. US 1992-981947, filed on 24 Nov 1992, now abandoned which is a continuation of Ser. No. US 1991-701464, filed on 15 May 1991, now abandoned
DT Utility
FS Granted
LN.CNT 462
INCL INCLM: 424/070.700
INCLS: 424/063.000
NCL NCLM: 424/070.700
NCLS: 424/063.000
IC [6]
ICM: A61K007-02
ICS: A61K007-06
EXF 424/401; 424/70; 424/63; 424/64; 424/70.7
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 4 OF 7 USPATFULL
AN 95:27447 USPATFULL
TI Chemical prevention or reversal of cataract by phase separation inhibitors
IN Clark, John I., Seattle, WA, United States

Fowler, Kerry W., Seattle, WA, United States
Orme, Mark W., Seattle, WA, United States
Theodore, Louis J., Lynnwood, WA, United States4)
PA Oculon Corporation, Cambridge, MA, United States (U.S. corporation)
PI US 5401880 19950328
AI US 1992-817280 19920102 (7)
RLI Continuation-in-part of Ser. No. US 1991-725045, filed on 3 Jul 1991, now abandoned which is a continuation-in-part of Ser. No. US 1990-633482, filed on 27 Dec 1990, now abandoned which is a continuation-in-part of Ser. No. US 1989-451955, filed on 15 Dec 1989, now abandoned which is a continuation-in-part of Ser. No. US 1988-198850, filed on 26 May 1988, now abandoned which is a continuation-in-part of Ser. No. US 1987-58140, filed on 4 Jun 1987, now abandoned
DT Utility
FS Granted
LN.CNT 1786
INCL INCLM: 564/159.000
INCLS: 548/146.000; 558/445.000; 560/147.000; 564/158.000
NCL NCLM: 564/159.000
NCLS: 548/146.000; 558/445.000; 560/147.000; 564/158.000
IC [6]
ICM: C07C235-34
ICS: C07C235-06; C07C255-29; C07D277-10
EXF 548/146; 558/445; 560/147; 564/158; 564/159; 514/365; 514/528; 514/550; 514/616
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 5 OF 7 USPATFULL
AN 94:70830 USPATFULL
TI Chemical prevention or reversal of cataract by phase separation inhibitors
IN Clark, John I., Seattle, WA, United States
Thurston, George M., Belmont, MA, United States
Li, Xiao-Yan, Arlington, MA, United States
PA Oculon Corporation, Cambridge, MA, United States (U.S. corporation)
PI US 5338545 19940816
AI US 1992-868288 19920413 (7)
RLI Continuation-in-part of Ser. No. US 1992-840058, filed on 21 Feb 1992, now abandoned And Ser. No. US 1989-451955, filed on 15 Dec 1989, now abandoned , said Ser. No. 840058 which is a continuation of Ser. No. US 1989-451350, filed on 15 Dec 1989, now patented, Pat. No. US 5091421 which is a continuation-in-part of Ser. No. US 1988-198850, filed on 26 May 1988, now abandoned which is a continuation-in-part of Ser. No. US 1987-58140, filed on 4 Jun 1987, now abandoned , said Ser. No. 451955 which is a continuation-in-part of Ser. No. 198850
DT Utility
FS Granted
LN.CNT 1559
INCL INCLM: 424/094.100
INCLS: 514/912.000
NCL NCLM: 424/094.100
NCLS: 514/912.000
IC [5]
ICM: A61K037-48
EXF 514/616; 514/25; 514/912; 424/94.1
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 6 OF 7 USPATFULL
AN 92:15047 USPATFULL
TI Chemical prevention or reversal of cataract by phase separation inhibitors
IN Clark, John I., Seattle, WA, United States
Benedek, George B., Belmont, MA, United States

Siezen, Roelant J., Ede, Netherlands
Thomson, John A., Laramie, WY, United States
Friedman, Simon H., Chicago, IL, United States
PA Massachusetts Institute of Technology, Cambridge, MA, United States (U.S. corporation)
PI US 5091421 19920225
AI US 1989-451350 19891215 (7)
RLI Continuation-in-part of Ser. No. US 1988-198850, filed on 26 May 1988, now abandoned which is a continuation-in-part of Ser. No. US 1987-58140, filed on 4 Jun 1987, now abandoned
DT Utility
FS Granted
LN.CNT 1386
INCL INCLM: 514/616.000
INCLS: 514/912.000
NCL NCLM: 514/616.000
NCLS: 514/912.000
IC [5]
ICM: A61K031-16
EXF 514/616; 514/912
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L3 ANSWER 7 OF 7 USPATFULL
AN 89:63090 USPATFULL
TI Modified silicone rubber and its use as a material for optical lenses and optical lenses made from this material
IN Schafer, Horst, Aschaffenburg, Germany, Federal Republic of
Kossmehl, Gerhard, Berlin, Germany, Federal Republic of
Neumann, Walter, Konigsbronn, Germany, Federal Republic of
PA Ciba-Geigy Corporation, Ardsley, NY, United States (U.S. corporation)
PI US 4853453 19890801
AI US 1987-135512 19871218 (7)
RLI Continuation of Ser. No. US 1986-863136, filed on 14 May 1986, now abandoned
PRAI DE 1985-3517612 19850515
DT Utility
FS Granted
LN.CNT 767
INCL INCLM: 528/028.000
INCLS: 525/474.000; 351/160.000H; 351/159.000
NCL NCLM: 528/028.000
NCLS: 351/159.000; 351/160.000H; 525/474.000
IC [4]
ICM: C08B077-06
EXF 528/28; 525/474; 351/160H; 351/159
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L5 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:754547 CAPLUS
DN 137:277784
TI Subtilisin protease and variants with reduced allergenicity for use in pharmaceutical, cleaning and cosmetic products
IN Estell, David A.; Ganshaw, Grant C.; Harding, Fiona A.; Larenas, Edmund A.; Poulose, Ayrookaran J.; Sikorski, Elizabeth Ellen; Elliott, Russel Philip
PA Genencor International, Inc., USA; The Procter & Gamble Company
SO PCT Int. Appl., 90 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2002077187 | A2 | 20021003 | WO 2002-US9205 | 20020322 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRAI US 2001-278459P P 20010323

L5 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:707187 CAPLUS
DN 137:237732
TI Ophthalmic solutions containing stabilized panthenol
IN Hattori, Manabu; Koide, Misao
PA Lion Corp., Japan
SO Jpn. Kokai Tokkyo Koho, 6 pp.
CODEN: JKXXAF
DT Patent
LA Japanese
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI JP 2002265357 | A2 | 20020918 | JP 2001-116095 | 20010312 |
| PRAI JP 2001-116095 | | 20010312 | | |

L5 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:594714 CAPLUS
DN 137:145641
TI Composition for treatment and/or care of the eye
IN Wagenaar, Louis Johan
PA Neth.
SO PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| PI WO 2002060495 | A1 | 20020808 | WO 2002-NL12 | 20020109 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ,
UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH,
CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRAI NL 2001-1017060 A 20010109
RE.CNT 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 2002:539563 CAPLUS
DN 137:99021
TI **Contact lens** care solutions containing dexpanthenol
IN Schwind, Peter; Scherer, Anton
PA Novartis Ag, Switz.; Novartis-Erfindungen Verwaltungsgesellschaft M.B.H.
SO PCT Int. Appl., 14 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | WO 2002055118 | A1 | 20020718 | WO 2002-EP231 | 20020111 |
| | W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TN, TR, TT, UA, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| | RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR | | | | |
| | US 2002155961 | A1 | 20021024 | US 2002-44373 | 20020111 |
| PRAI | EP 2001-100764 | A | 20010112 | | |
| | CH 2001-1035 | A | 20010607 | | |

RE.CNT 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2003 ACS
AN 1989:44975 CAPLUS
DN 110:44975
TI Preparation of modified silicone rubber for contact and intraocular lenses
IN Schaefer, Horst; Kossmehl, Gerhard; Neumann, Walter
PA Titmus Eurocon Kontaktlinsen G.m.b.H. und Co. K.-G., Fed. Rep. Ger.
SO Ger. Offen., 16 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 1

| | PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|---|
| PI | DE 3517612 | A1 | 19870102 | DE 1985-3517612 | 19850515 |
| | EP 205888 | A1 | 19861230 | EP 1986-106543 | 19860514 |
| | EP 205888 | B1 | 19891123 | | |
| | R: CH, DE, FR, GB, IT, LI, SE | | | | |
| | JP 62011717 | A2 | 19870120 | JP 1986-111771 | 19860515 |
| | CA 1274037 | A1 | 19900911 | CA 1986-509223 | 19860515 |
| | US 4853453 | A | 19890801 | US 1987-135512 | 19871218 |
| PRAI | DE 1985-3517612 | | 19850515 | | |
| | US 1986-863136 | | 19860514 | | |

-------claim tree-----------

1----2----4
+-----6----7----10
+-----3

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8----9

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claim# 3 contains the word -> prefer
claim# 4 contains the word -> prefer

--------best-----------
6187264
6172017
5422073
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6143799
5281277
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5672213
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5011661
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Re32672
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6331289
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6440911++++++++
6261537
6500463
3908680
3912451

-------classlist----------

422/28
514/840
514/839
134/901
510/112
424/7826
134/26
134/42
510/480
510/504
510/378
510/391
510/108
424/7836
134/3
510/424
510/303
510/113
510/477
15/10493
510/115
422/5
424/660
424/405
422/1
424/450
514/912
424/732
435/188
424/121
424/96
424/952
514/539
510/114
514/635
424/657
514/915
424/7804
424/94

--------keywords---------------

contact lenses contact lens panthenol penthenols dexpanthenol provitamin b5 pantothenyl constituent EDTA potassium chloride potassium sodium chloride viscosity surface-active buffer lens dexpanthenol D-sorbit tonicity antimicrobial PHMB g/l aqueous substances compounds sodium chloride NaCl KCl disinfecting disinfect sodium perborate perborate disodium cellulose ether Formulation dissolving rinse preservatives ingredient heavy powder gels phosphate TRIS sodium bicarbonate bicarbonate potassium citrate citrate citric acid citric sodium borate boric acid sulfonates acetates borates organic acids water-soluble salt water-soluble polymers polymers water-soluble ammonium salts quaternary ammonium quaternary sodium salts tetraacetic acid ethylenediamine tetraacetic tetraacetic ethylenediamine polyacrylic acid polyacrylic hydroxyethyl cellulose hydroxyethyl methyl cellulose cellulose polyvinyl alcohol polyvinyl Pluronic copolymers polyethylene sugar propylene glycol propylene urea glycerol inorganic organic formulate
d severe cleansing skin sorbitol constituent EDTA potassium chloride potassium sodium chloride viscosity surface-active buffer Schwind Peter Lens dexpanthenol disinfecting lenses Inventors Hosbach-Rottenberg Scherer Anton Frammersbach Address HOXIE NOVARTIS DEPT MORRIS AVENUE SUMMIT Intern DateCodeApplication D-sorbit tonicity antimicrobial PHMB g/l NaCl KCl disinfect pantothenic Provitamin D-pantothenyl D-panthenol healing wounds medicinal stabilises lachrymal inserting Vortex motion insertion eruption losses guards dryness enzymatic variable isotonic damaged isotonicity milliosmol mannitol poloxamer glycol--polypropylene miranol hydroxypropylmethyl abbreviated biguanides hexamethylene polyaminopropyl biguanide polyhexamethylene ophthalmologically hydrochlorides hydrobromides gluconates maleates ascorbates tartrates trometamol buffers NaH hexavalent D-sorbitol D-glucitol moisture-retaining plasticiser sorbit aqueous substances compounds sodium chloride alcohol acid liquid prevents fluid glycol Mixtures RTM m
ethyl hydrogen salts ammonium ether salt above-mentioned ppm mixing
--------references-------------

---------- 6187264
classes:1 422/28 1 514/839 1 514/840
score: 833

keywords: contact lenses;contact lens;potassium chloride;potassium;sodium chloride;lens;antimicrobial;aqu
eous;substances;compounds;sodium;chloride;disinfecting;disinfect;Formulation;preservatives;powder;citric
acid;citric;boric acid;water-soluble;polyethylene;inorganic;organic;formulated;sorbitol;potassium chlorid
e;potassium;sodium chloride;Lens;disinfecting;lenses;Inventors;antimicrobial;disinfect;isotonic;abbreviat
ed;biguanide;buffers;aqueous;substances;compounds;sodium;chloride;acid;liquid;glycol;hydrogen;salts;salt;
above-mentioned;ppm;acids;boric;comfort;kinds;store;storing;

- , more preferably from 0.5 to
2.0% by weight. Lavish use of **sodium chloride**, in particular, should be
avoided because it tends to lessen the antimicrobial effect of polylysine
if added in concentrations exceeding 3.0%.
Examples of useful isotonic components include **inorganic** acid salts, such
as **sodium chloride**, **potassium chloride**, and magnesium chloride; acids,
such as hydrochloric acid, acetic acid, and **citric** acid; and alkalis, such
as sodium hydroxide and sodium citrate. Substances generally known as a
**buffer**, such as **boric acid**, borax, sodium phosphate, and sodium phosphite,
can also be used as an isotonic component either alone or in combination.
In particular, **boric acid** is capable of pH adjustment, and its aqueous
solution is useful as a disinfectant that can be used with safety as is
seen from its current application to disinfection in the treatment of eye
diseases and throat diseases. Accordingly, it is also expected to ha
- ns in the
form of various tablets including effervescent **water-soluble** tablets and
non-effervescent **water-soluble** tablets, powders, and granules.
Polylysine as obtained in the form of a thick aqueous solution can be
**formulated** into various tablets, powders or granules together with the
above-mentioned salts, acids, etc. for obtaining isotonic properties, such
as **sodium chloride**, **potassium chloride**, magnesium chloride, hydrochloric
acid, **citric** acid, sodium citrate, **boric acid**, borax, and sodium primary
phosphate. These polylysine preparations can also be prepared by using
appropriate inert ingredients customarily used in the preparation of
**water-soluble** tablets, powders and granules, such as carriers, lubricants,
crystal agents or vehicles, e.g., **polyethylene** glycol, dextran, lactose,
crystalline **cellulose**, etc.
Where polylysine is **formulated** together with an effervescent salt, such as
a mixture of **citric** acid or tartaric acid

---------- 6172017
classes:1 510/112 1 510/470 1 510/474
score: 827

keywords: contact lenses;contact lens;EDTA;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;di
sinfecting;disinfect;disodium;Formulation;rinse;powder;phosphate;sodium borate;polymers;ammonium salts;qu
aternary ammonium;quaternary;propylene glycol;propylene;glycerol;organic;sorbitol;EDTA;buffer;Lens;disinf
ecting;lenses;tonicity;antimicrobial;disinfect;insertion;enzymatic;isotonic;mannitol;biguanides;hexamethy
lene;buffers;aqueous;compounds;sodium;alcohol;acid;glycol;Mixtures;hydrogen;salts;ammonium;salt;efficacy;
boric;borate;gas-permeable;soak;

- . 4,614,549,
which is incorporated herein by reference.
The compositions of the present invention can be prepared in various
physical forms, such as liquids, solids, emulsions or colloidal
suspensions. For example, the carbohydrates and additional ophthalmologic
ingredients can be dissolved or suspended in a suitable solvent such as
water, **glycerol**, **propylene glycol** or the like so long as such carriers and
ingredients are compatible with direct insertion into the eye, where such
is the intended regimen. Alternatively, the composition can be in the form
of a powder or tablet wherein the latter will typically contain binders or
other tablet excipients.
The following detailed examples are presented to illustrate the present
invention. Both ambient and thermal cleaning processes are performed on
the indicated lenses, identified by FDA group characteristics.
EXAMPLE 1
Ten SoftMate.RTM. B lenses manufactured by Sola/Barnes-Hind of bufilc
- ts of 0.85% **boric acid**, 0.09% **sodium borate** and 0.45% sodium

chloride. Cleaning results are reported in Table 1.

TABLE 1

Simultaneous Cleaning and Thermal Disinfection of Bufilcon Group 3 Contact Lenses

| Cleaning Compound | Conc. [%] | Residual Protein on Lens [.mu.g/lens] | Increased Removal Over Control [%] |
|---|---|---|---|
| **sorbitol** | 1% | 10.69 | 58.4 |
| Glucose | 1% | 18.76 | 27.1 |
| Borate **buffer**ed -- Saline (Control) | -- | 25.72 | -- |

EXAMPLE 2

A seven cycle ambient cleaning efficacy test is performed for ten new Vistamarc (FDA Group IV) contact lenses, manufactured by Johnson & Johnson Vision Products Inc. of Etaficon A polymer having a 58% water content. The lenses are soaked for one hour in lysozyme at 37.degree. C. in order to deposit protein on the lenses, simulating lens wear. Each lens is placed in 10

- BS), at a pH of 7.0-7.3 and osmolality of 280-320 mOsm/kg., as described in Example 1. Cleaning results are report in Table 3.

TABLE 3

Contact Lens Cleaning Efficacy for Various FDA Group Lens

| Test Compound | FDA Lens Group | .mu.g Protein Per Lens | Increased Removal Over Control [%] |
|---|---|---|---|
| 1% **sorbitol** in BBS | II | 13 | 32 |
| BBS Control | II | 19 | -- |
| 1% **sorbitol** in BBS.sup.1 | III | 5 | 54 |
| BBS Control | III | 11 | -- |
| 1% **sorbitol** in BBS | IV | 682 | 18 |
| BBS Control | IV | 827 | -- |
| 1% **sorbitol** + 0.025% EDTA.sup.2 in BBS | III | 7 | 36 |
| BBS Control & EDTA | III | 11 | -- |

.sup.1 Borate **buffer**ed Saline

.sup.2 **ethylenediamine**tetracetic acid, disodium salt

EXAMPLE 4

SoftMate.RTM. B contact lenses are soaked in a protein deposi

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---------- 5422073

classes:1 422/28 1 134/901 1 424/7826 1 424/7836 1 514/839 1 514/840

score: 802

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citric acid;citric;sodium borate;boric acid;water-soluble;tetraacetic acid;tetraacetic;hydroxyethyl;copolymers;polyethylene;propylene;glycerol;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;NaCl;disinfect;isotonic;isotonicity;biguanide;polyhexamethylene;ophthalmologically;buffers;aqueous;compounds;sodium;chloride;acid;Mixtures;hydrogen;salts;ammonium;salt;ppm;acids;efficacy;citrates;boric;borate;adjust;

- Angus Chemical Company it is disclosed that TRIS AMINO holds the pH of contact lens cleaning solutions in the range most favorable for hydrolysis of protein films on lens surfaces, and that the lack of eye irritancy of TRIS AMINO are of prime consideration in its choice for this application. However the ANGUS technical bulletin fails to disclose use of tromethamine in formulating contact lens disinfecting solutions, the fact that tromethamine has microbicidal properties, nor the fact that tromethamine has a synergistic effect when combined with other microbicides.

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or **water-soluble** salts thereof, including ethylene diamine **tetraacetic** acid, nitrilo triacetic acid, diethylene triamine pentaacetic acid, **hydroxyethyl** ethylene diamine triacetic acid, 1,2-diaminocyclohexane **tetraacetic** acid, ethylene glycol bi

- s (beta-aminoethyl ether) in N, N, N', N' **tetraacetic** acid (EGTA), amino diacetic acid and **hydroxyethyl** amino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tri- and

tetra-sodium salts of ethylene diamine **tetraacetic** acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include **citric** acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphtes, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and **potassium** salts as well as the ammonium salt.

The pH

- in providing lubrication to the eye. Suitable tonicity agents include **sodium chloride**, **potassium chloride**, **glycerol** or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.5 weight percent **sodium chloride**.

Suitable surfactants include tyloxapol, which is 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane; **Pluronic**.RTM. or poloxamers, nonionic block copolymer surfactants which are block **copolymers** of **propylene** oxide and ethylene oxide; octoxynol or octyphenoxy polyethoxyethanol prepared by reacting isooctylphenol with ethylene oxide; poloxamine which is a block copolymer derivative of ethylene oxide and **propylene** oxide combined with ethylene diamine; and nonoxynol nonionic surfa

- ctant mixtures prepared by reacting nonylphenols with ethylene oxide. Most of these surfactants am described in the Merck Index, supra. The surfactants can be employed in amounts ranging from about 0.0001 to about 20% by weight, preferably from about 0.005 to about 5.0% by weight, more preferably from about 0.025 to about 1 percent by weight. In one embodiment 250 ppm of tyloxapol is used.

Suitable **viscosity** inducing agents can include lecithin or the **cellulose** derivatives such as hydroxymethylcellulose, hydroxypropylcellulose and methylcellulose in amounts similar to those for surfactants, above.

If solid dosage forms are used, the formulations may include conventional lubricants, binders, and excipients which include, but are not limited to **glycerol**, **sorbitol**, **propylene glycol**, **polyethylene** glycols and dextran. These materials are used in amounts varying between 0.001 and 30% by weight, preferably between about 0.1 and 5 percent.

- vigorously agitated and one mi. aliquots withdrawn and dispensed into 9 ml of neutralizing broth. Ten-fold serial dilutions of each inoculated solution were prepared in neutralizing broth. The solutions were plated out at effective dilutions of 1/10th to 1/100,000th on nutrient agar with or without neutralizing agents. The plates were incubated under optimal conditions of time and temperature for growth and the colonies counted.

The concentration of the survivors and the log reductions were calculated. Each ten-fold decrease in concentration constitutes a one-log reduction.

EXAMPLE 1

This example illustrates the surprising efficacy of tromethamine in an isotonic aqueous solution as a microbicide that is effective against difficult-to-kill organisms.

| | Isotonic aqueous |
|---|---|
| Example 1A: | solution containing tromethamine. |
| Tromethamine | 1.2 |

---------- 5500186

classes:1 422/28 1 134/901 1 424/7826 1 424/7836 1 514/839 1 514/840

score: 780

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citric acid;citric;sodium borate;boric acid;water-soluble;tetraacetic acid;tetraacetic;hydroxyethyl;copolymers;polyethylene;propylene;glycerol;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;NaCl;disinfect;isotonic;isotonicity;biguanide;polyhexamethylene;ophthalmologically;buffers;aqueous;compounds;sodium;chloride;acid;Mixtures;hydrogen;salts;ammonium;salt;ppm;acids;efficacy;citrates;boric;borate;adjust;

- eye

irritancy of TRIS AMINO are of prime consideration in its choice for this application. However the ANGUS technical bulletin fails to disclose use of tromethamine in formulating contact lens disinfecting solutions, the fact that tromethamine 10 has microbicidal properties, nor the fact that tromethamine has a synergistic effect when combined with other microbicides.

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or **water-soluble** salts thereof, including ethylene diamine **tetraacetic** acid, nitrilo triacetic acid, diethylene triamine pentaacetic acid, **hydroxyethyl** ethylene diamine triacetic acid, 1,2-diaminocyclohexane **tetraacetic** acid, ethylene glycol his (beta-aminoethyl ether) in N, N, N', N'tetraacetic acid (EGTA), amino diacetic acid and **hydroxyethyl** amino diacetic acid. These acids can be used in the form of their water soluble salts, particula

- rly their alkali

metal salts. Especially preferred chelating agents are the di-, tri- and tetra-sodium salts of ethylene diamine **tetraacetic** acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include **citric** acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphtes, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and **potassium** salts as well as the ammonium salt.

The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.3 to 7.7. Significant deviations from neu

- present invention may contain additional

ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and **viscosity** inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include **sodium chloride**, **potassium chloride**, **glycerol** or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.5 weight percent **sodium chloride**.

Suitable surfactants include tyloxapol, which is 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane; **Pluronic**.RTM. or poloxamers, nonionic block copolymer surfactants which are block **copolymers** of **propylene** oxi

- out 0.0001 to about 20% by weight, preferably from about 0.005 to about 5.0% by weight, more preferably from about 0.025 to about 1 percent by weight. In one embodiment, 250 ppm of tyloxapol is used.

Suitable **viscosity** inducing agents can include lecithin or the **cellulose** derivatives such as hydroxymethylcellulose, hydroxypropylcellulose and methylcellulose in amounts similar to those for surfactants, above.

If solid dosage forms are used, the formulations may include conventional lubricants, binders, and excipients which include, but are not limited to **glycerol**, **sorbitol**, **propylene glycol**, **polyethylene** glycols and dextran. These materials are used in amounts varying between 0.001 and 30 % by weight, preferably between about 0.1 and 5 percent.

The preferred aqueous solutions of the invention can be prepared by adding the ingredient as follows. Add the tromethamine to water. Adjust the pH of the solution to a pH from about 6.8 to about 7

---------- 5756045
classes:1 422/28 1 134/901 1 424/7826 1 424/7836 1 514/539 1 514/840
score: 768

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citric acid;citric;sodium borate;boric acid;water-soluble;tetraacetic acid;tetraacetic;hydroxyethyl;copolymers;polyethylene;propylene;glycerol;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;NaCl;disinfect;isotonic;isotonicity;biguanide;polyhexamethylene;ophthalmologically;buffers;aqueous;compounds;sodium;chloride;acid;Mixtures;hydrogen;salts;ammonium;salt;ppm;acids;efficacy;citrates;boric;borate;adjust;soak;

- patible with, and has little or no undesirable chemical

reactions with hydrophilic contact lenses. Another advantage of the present invention is that it provides a method and a composition for disinfecting contact lenses which has a low potential for irritating the eyes. And still yet another advantage of the present invention is that in certain embodiments, it provides a method and composition for disinfecting contact lenses, for cleaning tear film debris from contact lenses, and for lubricating contact lenses.

Tromethamine, whose chemical name is 2-amino-2-hydroxymethyl-1,3-propanediol, is also known by names of trimethylol aminomethane; tris(hydroxymothyl)aminomethane; trisamine; tris **buffer**; trometamol; Tromethane; THAM; TRIS; Talatrol; Tris Amino; Tris-steril; Trizma as described in the Merck Index, Eleventh Edition, Published by Merck & Co., Inc. Rahway, N.J. (1989). Trometharnine and its salts act as **buffer**s over t

- aacetic acid, **hydroxyethyl** ethylene diamine triacetic acid, 1,2-diaminocyclohexane **tetraacetic** acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' **tetraacetic** acid (EGTA), amino diacetic acid and **hydroxyethyl** amino diacelic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tri- and tetra-sodium salts of ethylene diamine **tetraacetic** acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include **citric** acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphtes, tetraphosphates, trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form o

- f the neutral or acidic alkali metal salts such as the sodium and **potassium** salts as well as the ammonium salt.

The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.3 to 7.7. Significant deviations from neutral (pH=7) will cause changes in the physical parameters (ie. diameter) in some contact lenses. Low pH (pH less than 5.5) can cause burning and stinging of the eyes, while very low or very high pH (less than 3.0 or greater than 10) can cause ocular damage.

The term "disinfect" means the rendering non-viable of substantially all pathogenic microbes that are in the vegetative state, including gram negative and gram positive bacteria, as well as fungi.

The additional microbicides employed in the present invention are known, such as polyhexamethylene biguanide, N-alkyl-2-pyrrolidone, chlorhexidine, polyhexamethyleneb

- lier, such as tonicity agents, surfactants and **viscosity** inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include **sodium chloride**, **potassium chloride**, **glycerol** or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.5 weight percent **sodium chloride**.

Suitable surfactants include tyloxapol, which is 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane; **Pluronic**.RTM. or poloxamers, nonionic block copolymer surfactants which are block **copolymers** of **propylene** oxide and ethylene oxide; octoxynol or octyphenoxy polyethoxyethanol prepared by reacting isooctylphenol with ethylene oxide; poloxamine which is a block

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---------- 6162393
classes:1 422/28 1 424/405 1 424/732 1 514/839 1 514/840
score: 768

keywords: contact lenses;contact lens;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antimicrobial;aqueous;substances;compounds;sodium;chloride;disinfecting;disinfect;Formulation;rinse;preservatives;ingredient;phosphate;polymers;cellulose;polyvinyl;Pluronic;polyethylene;propylene;severe;skin;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;Inventors;tonicity;antimicrobial;disinfect;isotonic;mannitol;buffers;aqueous;substances;compounds;sodium;chloride;acid;Mixtures;hydrogen;ammonium;ppm;boric;borate;adjust;comfort;meanings;

- major solute in human tears. In addition **propylene glycol**, lactulose,

trehalose, **sorbitol**, mannitol or other osmotic agents may also be added to replace some or all of the **sodium chloride**. Also, various **buffer** systems such as citrate, phosphate (appropriate mixtures of Na.sub.2 HPO.sub.4, NaH.sub.2 PO.sub.4, and KH.sub.2 PO.sub.4), borate (boric acid, sodium borate, **potassium** tetraborate, **potassium** metaborate and mixtures), bicarbonate, and tromethamine and other appropriate nitrogen-containing **buffer**s (such as ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, MES, MOPS, PIPES, TAPS, TES, Tricine) can be used to ensure a physiologic pH between about pH 6.5 and 8.5.

Various **viscosity** building agents such as **polyethylene** glycol, surfactants, **polyvinyl**pyrrolidone, **polyvinyl alcohol**, carboxymethyl **cellulose** and similar materials may be added to adjust the "body" and "feel" of the solution. Surface active a

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---------- 5928606

classes:1 422/28 1 206/205 1 206/3161 1 422/292 1 422/294 1 422/300 1 424/409 1 514/839

score: 763

keywords: contact lenses;contact lens;potassium;buffer;lens;tonicity;PHMB;aqueous;sodium;chloride;NaCl;disinfecting;disinfect;phosphate;citrate;boric acid;water-soluble salt;water-soluble;quaternary ammonium;quaternary;polyacrylic acid;polyacrylic;cellulose;polyvinyl alcohol;polyvinyl;Pluronic;copolymers;propylene glycol;propylene;severe;potassium;buffer;Lens;disinfecting;lenses;tonicity;PHMB;NaCl;disinfect;biguanide;polyhexamethylene;buffers;aqueous;sodium;chloride;alcohol;acid;liquid;glycol;ammonium;salt;mixing;toxicity;efficacy;boric;borate;comfort;correspond;kinds;disinfectants;storing;

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- e borate **buffer** includes 2.0% of **boric acid** and 0.03% of borax, and has a pH of about 7.2, for example.

It is preferable that the **buffer** used as the wetting agent further contain a surface active agent. One example of the surface active agent to be contained in the **buffer** is a block polymer-type nonionic surface active agent which is formed by addition polymerization of ethylene oxide as a hydrophilic group, with polypropylene glycol as a lipophilic group obtained by polymerization of **propylene** oxide, such that the ethylene oxide is bonded to both ends of the polypropylene glycol. Examples of such a block polymer-type nonionic surface active agent are "Pluronic P123", "Pluronic P85", "PEP-101", "Pluronic F68" and "Pluronic F127" (all available from BASF CORPORATION, U.S.A.). Other examples of the non-ionic surface active agent are POE(60) hardened castor oil, POE(40) **sorbitol** tetraoleate and polyglycerin fatty acid ester.

When

- e **buffer**, the following cleaning procedure is effected before, during or after the disinfecting treatment according to the present invention, whereby the contact lens can be cleaned and disinfected at the same time in a simplified manner. Described more specifically, as in the disinfecting method of the present invention, the contact lens is held by and between the receptacle 2 and the cover 6 of the disinfecting device 10 as described above. With the contact lens kept in contact with the two members, the cover 6 is slidably rotated with respect to the receptacle 2. According to this procedure, the opposite surfaces of the contact lens are rubbed between the contacting surfaces (portions) of the receptacle 2 and cover 6 of the disinfecting device 10, which contacting surfaces are provided by the soft material. Thus, the present contact lens cleaning and disinfecting device provides the same or even greater cleaning effect, as
- by

the present invention. As the chelating agent, sodium edetate, trihydroxymethylaminomethane, sodium polyphosphate, sodium pyrophosphate, sodium citrate, 1-hydroxyethane-1,1-diphosphonic acid or tetrasodium salt of 1-hydroxyethane-1,1-diphosphonic acid is used, for example. 25 Examples of the tonicity agent are **sodium chloride**, **potassium chloride**, sodium bicarbonate, polyhydric alcohols such as glycerin and **propylene glycol**, and saccharides such as glucose and mannitol. It is particularly preferable to use the glycerin and **propylene glycol** as the tonicity agent. The glycerin or **propylene glycol** is used in an amount that controls the osmotic pressure to about 300 mOsm. Examples of the preservative are Paraben (parahydroxybenzoic acid), basic nitrogen, sorbic acid, **potassium** sorbate, sodium benzoate, a guanidine preservative, and a **quaternary** ammonium salt preservative. As the disinfectant, chlorhexidine gluconate

- o
- owing manner by respectively using, as the soft material, an unwoven fabric of acrylic acid copolymer, a **polyvinyl**formal sponge, and a **cellulose** sponge, so as to examine whether these materials are suitable as the soft material.

Described more specifically, the specimens Nos. 1-3 of the contact lens disinfecting device consisting of the receptacle 2 and the cover 6 as shown in FIGS. 1A through 3 were prepared by respectively using, as the soft material, the unwoven fabric of acrylic acid copolymer, **polyvinyl**formal sponge, and **cellulose** sponge. The receptacle 2 and cover 6 of each disinfecting device 10 were boiled in distilled water for 30 minutes. This boiling operation was repeated twice. Next, the disinfecting device 10 subjected to the boiling operation was immersed for one hour in a disinfectant solution, which is a solution of polyhexamethylene biguanide hydrochloride salt (PHMB) having a concentration of 1000 ppm.

---------- 5593637
classes:1 422/28 1 134/901 1 424/7826 1 424/7836 1 514/839 1 514/840
score: 760

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;PHMB;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citric acid;citric;sodium borate;boric acid;water-soluble;tetraacetic acid;tetraacetic;hydroxyethyl;copolymers;polyethylene;propylene;glycerol;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;PHMB;NaCl;disinfect;isotonic;isotonicity;biguanide;polyhexamethylene;ophthalmologically;buffers;aqueous;compounds;sodium;chloride;acid;Mixtures;hydrogen;salts;ammonium;salt;ppm;acids;efficacy;citrates;boric;borate;adjust;

- r film debris from contact lenses, and for lubricating contact lenses.

Tromethamine, whose chemical name is 2-amino-2-hydroxymethyl-1,3-propanediol, is also known by names of trimethylol aminomethane; tris(hydroxymethyl)aminomethane; trisamine; tris **buffer**; trometamol; Tromethane; THAM; TRIS; Talatrol; Tris Amino; Tris-steril; Trizma as described in the Merck Index, Eleventh Edition, Published by Merck & Co., Inc. Rahway, N.J. (1989). Tromethamine and its salts act as **buffer**s over the pH range of 6-9. In the ANGUS Chemical Company Technical Bulletin TB 69. TRIS AMINO.RTM. as a **buffer** for pH control, Angus Chemical Company it is disclosed that TRIS AMINO holds the pH of contact lens cleaning solutions in the range most favorable for hydrolysis of protein films on lens surfaces, and that the lack of eye irritancy of TRIS AMINO are of prime consideration in its choice for this application. However the ANGUS technical bulleti

- n fails to disclose use of tromethamine in formulating contact lens disinfecting solutions, the fact that tromethamine has microbicidal properties, nor the fact that tromethamine has a synergistic effect when combined with other microbicides.

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or **water-soluble** salts thereof, including ethylene diamine **tetraacetic** acid, nitrilo triacetic acid, diethylene triamine pentaacetic acid, **hydroxyethyl** ethylene diamine triacetic acid, 1,2-diaminocyclohexane **tetraacetic** acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' **tetraacetic** acid (EGTA), amino diacetic acid and **hydroxyethyl** amino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tri- and tetra-sodium salts of ethylene diamine

- d contain the tromethamine or salt thereof, the microbicide, and the chelating agent. Prior to use, the tablet is dissolved in the diluent, eg. water or saline to form a solution for disinfecting contact lenses. Another embodiment would be an aqueous solution comprising the novel disinfecting ingredients.

A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and **viscosity** inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include **sodium chloride**, **potassium chloride**, **glycerol** or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophil

- rcent by weight. In one embodiment, 250 ppm of tyloxapol is used.

Suitable **viscosity** inducing agents can include lecithin or the **cellulose** derivatives such as hydroxymethylcellulose, hydroxypropylcellulose and

methylcellulose in amounts similar to those for surfactants, above.
If solid dosage forms are used, the formulations may include conventional lubricants, binders, and excipients which include, but are not limited to **glycerol**, **sorbitol**, **propylene glycol**, **polyethylene** glycols and dextran. These materials are used in amounts varying between 0.001 and 30% by weight, preferably between about 0.1 and 5 percent.
The preferred aqueous solutions of the invention can be prepared by adding the ingredient as follows. Add the tromethamine to water. Adjust the pH of the solution to a pH from about 6.8 to about 7.8. Add the chelating agent and the tonicity agent, if required. Stir to dissolve the above ingredients. Optionally, add the surfa
- ctant and the **viscosity** inducing agent. Add the microbicide. The final product can be rendered sterile by sterile filtration, heat sterilization or a combination thereof.
A suggested method for disinfecting a contact lens is as follows. The lenses are first rubbed with a few drops of the subject solution or saline and rinsed to remove surface contaminants such as mucous, eye makeup, etc., and then placed in a suitable container with a sufficient amount of the aqueous solution to cover the lenses. The lenses are allowed to soak for at least 10 minutes and up to 8 hours to achieve substantial kill of the microorganisms. The foregoing method is carried out at ambient or at elevated temperatures, ie. 20.degree. C. to about 100.degree. C.
To illustrate the manner in which the invention may be carried out, the following examples are given. It is understood, however, that the examples are for the purposes of illustration and the invention

---------- 5817277
classes:1 422/28 1 134/901 1 424/7826 1 424/7836 1 514/839 1 514/840
score: 739

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citric acid;citric;sodium borate;boric acid;water-soluble;tetraacetic acid;tetraacetic;hydroxyethyl;copolymers;polyethylene;propylene;glycerol;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;NaCl;disinfect;isotonic;isotonicity;biguanide;polyhexamethylene;ophthalmologically;buffers;aqueous;compounds;sodium;chloride;acid;Mixtures;hydrogen;salts;ammonium;salt;ppm;acids;efficacy;citrates;boric;borate;adjust;

- microbicides.
Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or **water-soluble** salts thereof, including ethylene diamine **tetraacetic** acid, nitrilo triacetic acid, diethylene triamine pentaacetic acid, **hydroxyethyl** ethylene diamine triacetic acid, 1,2-diaminocyclohexane **tetraacetic** acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N'tetraacetic acid (EGTA), amino diacetic acid and **hydroxyethyl** amino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tri- and tetra-sodium salts of ethylene diamine **tetraacetic** acid (EDTA), most preferably disodium EDTA (Disodium Edetate).
Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention i
- would be an aqueous solution comprising the novel disinfecting ingredients.
A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and **viscosity** inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include **sodium chloride**, **potassium chloride**, **glycerol** or mixtures thereof. The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.5 weight percent **sodium chloride**.
Suitable surfactants include tyloxapol, which is 4-(1,1,3,3-tetramethylbutyl)phenol polymer with formaldehyde and oxirane;

- unts similar to those for surfactants, above.
If solid dosage forms are used, the formulations may include conventional lubricants, binders, and excipients which include, but are not limited to

**glycerol**, **sorbitol**, **propylene glycol**, **polyethylene** glycols and dextran. These materials are used in amounts varying between 0.001 and 30% by weight, preferably between about 0.1 and 5 percent.

The preferred aqueous solutions of the invention can be prepared by adding the ingredient as follows. Add the tromethamine to water. Adjust the pH of the solution to a pH from about 6.8 to about 7.8. Add the chelating agent and the tonicity agent, if required. Stir to dissolve the above ingredients. Optionally, add the surfactant and the **viscosity** inducing agent. Add the microbicide. The final product can be rendered sterile by sterile filtration, heat sterilization or a combination thereof.

A suggested method for disinfecting a contact lens is as follows.

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---------- 5605661
classes:1 422/28 1 134/26 1 134/901 1 435/188 1 510/114 1 514/839
score: 719

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;preservatives;ingredient;phosphate;citrate;citric acid;citric;boric acid;water-soluble;quaternary ammonium;quaternary;copolymers;polyethylene;propylene;glycerol;inorganic;organic;formulated;sorbitol;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;NaCl;disinfect;enzymatic;biguanides;hexamethylene;biguanide;aqueous;compounds;sodium;chloride;acid;liquid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;ppm;mixing;acids;toxicity;efficacy;boric;borate;adjust;comfort;correspond;

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- ittle or no impact on the ionic strength of the disinfecting solution.

As used in the present specification, the term "low osmolality effect" is defined as an increase in osmolality of about 0-50 milliOsmoles/kg when 1 to 2 drops of the liquid enzyme composition is added to the diluent solution. Osmolality is an indirect measure of available H.sub.2 O hydrogen bonding and ionic strength of a solution. It is convenient to utilize osmolality measurements to define acceptable tonicity ranges for disinfecting solutions. As indicated above, the antimicrobial activity of disinfecting agents, particularly polymeric **quaternary ammonium** compounds such as polyquaternium-1, is adversely affected by high concentrations of **sodium chloride** or other ionic solutions.

The ionic strength or tonicity of the cleaning and disinfecting solution of the present invention has been found to be an important factor. More specifically, polymeric ammonium

- salts of chlorhexidine, hexamethylene biguanides and their **polymers**. The polymeric antimicrobial agents used herein are preferably employed in the absence of mercury-containing compounds such as thimerosal. The salts of alexidine and chlorhexidine can be either **organic** or **inorganic** and are typically gluconates, nitrates, **acetates**, phosphates, sulphates, halides and the like.

Particularly preferred are polymeric **quaternary ammonium** compounds of the structure:

##STR1##

wherein: R.sub.1 and R.sub.2 can be the same or different and are selected from:

N.sup.+ (CH.sub.2 CH.sub.2 OH).sub.3 X.sup.-, N(CH.sub.3).sub.2 or OH;

X is a pharmaceutically acceptable anion, preferably chloride; and

n is an integer from 1 to 50.

The most preferred compounds of this structure is polyquaternium-1, which is also known Onamer M.TM. (registered trademark of Onyx Chemical Corporation) or as Polyquad.RTM. (registered trademark of Alcon Laboratories, I

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---------- 4836986
classes:1 422/28 1 424/7804 1 510/112 1 510/475 1 510/499 1 514/635 1 523/122
score: 711

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antimicrobial;PHMB;aqueous;compounds;sodium;chloride;disinfecting;disodium;Formulation;dissolving;preservatives;ingredient;phosphate;sodium bicarbonate;bicarbonate;citrate;citric;sodium borate;boric acid;water-soluble salt;polymers;water-soluble;quaternary ammonium;quaternary;hydroxyethyl;cellulose;polyvinyl alcohol;polyvinyl;polyethylene;glycerol;organic;formulated;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;PHMB;isotonic;miranol;biguanides;hexamethylene;biguanide;polyhexamethylene;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;salt;ppm;toxicity;boric;borate;comfort;disinfectants;

- PHMB-containing solution of the present invention. Because of their demulcent effect, **viscosity** builders have a tendency to enhance the lens wearer's comfort by means of a film on the lens surface cushioning impact against the eye. Included among the **water-soluble viscosity** builders are the **cellulose polymers** like **hydroxyethyl** or hydroxypropyl **cellulose**, carboxymethyl **cellulose** and the like. Such **viscosity** builders may be employed in amounts ranging from about 0.01 to about 4.0 weight percent or less.

This invention relates to disinfecting and/or preserving solutions for use with most contact lenses, including hard and soft lenses, as well as the newer hard gas permeable type contact lenses, such as described in U.S. Pat. No. 4,327,203. The term "soft contact lens" as used herein generally refers to those contact lenses which readily flex under small amounts of force and return to their original shape when that force is re

- se of the PHMB **buffer** preservative system in ophthalmologic products and dermatologic formulations applied near the eye. Such use will, of course, depend upon the compatibility of the preservative system with the active ingredient(s) in the product.

The following examples demonstrate the compositions and methods of the instant invention. However, it is to be understood that these examples are for illustrative purposes only and do not purport to be wholly definitive as to conditions and scope of this invention.

EXAMPLE I

An aqueous contact lens disinfectant solution is prepared having the following formulation:

| | Percent (w/v) |
|---|---|
| Polyhexamethylene Biguanide HCl* | .0001 |
| Poloxamine 1107** | .5 |
| Na.sub.2 EDTA | .011 |
| **boric acid** | 1.10 |
| **sodium borate** | .40 |
| **sodium chloride** | .30 |

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6143799

classes:1 514/839 1 422/28 1 424/657 1 510/112 1 514/840 1 514/912 1 514/915

score: 706

keywords: contact lenses;contact lens;EDTA;potassium chloride;potassium;sodium chloride;viscosity;buffer;lens;antimicrobial;aqueous;compounds;sodium;chloride;disinfecting;disodium;Formulation;dissolving;preservatives;ingredient;gels;phosphate;citrate;citric acid;citric;sodium borate;boric acid;polymers;water-soluble;quaternary ammonium;quaternary;tetraacetic;hydroxyethyl cellulose;hydroxyethyl;cellulose;polyvinyl;Pluronic;sugar;propylene glycol;propylene;organic;formulated;EDTA;potassium chloride;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;antimicrobial;isotonic;mannitol;biguanides;biguanide;polyhexamethylene;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;glycol;Mixtures;salts;ammonium;mixing;acids;efficacy;boric;borate;comfort;gas-permeable;disinfectants;storing;

- ch as mannitol, glycerin or **propylene glycol**, in an aqueous solution. The resultant solution may then be used as a **buffer** and/or antimicrobial agent in aqueous ophthalmic compositions, even where such compositions also contain PVA. The borate-polyol complexes of the present invention are also useful in unpreserved saline solutions.

The borate-polyol complexes of the present invention are particularly useful as adjunctive disinfecting agents in contact lens disinfecting solutions containing monomeric **quaternary ammonium** compounds (e.g., benzalkonium chloride) or biguanides (e.g., chlorhexidine) or polymeric antimicrobials, such as polymeric **quaternary ammonium** compounds (e.g., Polyquad.RTM., Alcon Laboratories, Inc., Fort Worth, Tex.) or polymeric biguanides (e.g., Dymed.RTM., Bausch & Lomb, Rochester, N.Y.).

The compositions of the present invention may optionally contain PVA; such compositions are particularly useful in contact le

- e polyols can be linear or circular, substituted or unsubstituted, or mixtures thereof, so long as the resultant complex is **water-soluble** and pharmaceutically acceptable. Such compounds include **sugar**s, **sugar** alcohols, **sugar** acids and uronic acids. Preferred polyols are **sugar**s, **sugar** alcohols and **sugar** acids, including, but not limited to: mannitol, glycerin, **propylene glycol**

and **sorbitol**. Especially preferred polyols are mannitol and glycerin; most preferred is mannitol.

The **water-soluble** borate-polyol complexes of the present invention may be formed by mixing borate with the polyol(s) of choice in an aqueous solution. These complexes can be used in conjunction with other known preservatives and disinfectants to meet preservative efficacy and disinfection standards. In such compositions, the molar ratio of borate to polyol is generally between about 1:0.1 and about 1:10, and is preferably between about 1:0.25 and about 1:

- 0 wt %, preferably between about 0.1 and about 1.4 wt % and most preferably at a concentration of about 0.75 wt %.

EXAMPLE 1

The **water-soluble** borate-polyol complexes of the present invention may be prepared as illustrated below.

| FORMULATION (% weight/volume) INGREDIENT | A | B | C | D | E | F | G | H |
|---|---|---|---|---|---|---|---|---|
| **boric acid** | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 | 0.35 |
| **sodium borate** | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 | 0.11 |
| Mannitol | 0.5 | 1.0 | 1.5 | 2.0 | -- | -- | -- | -- |
| Glycerin | -- | -- | -- | -- | 0.5 | 1.0 | 1.5 | 2.0 |
| Na.sub.2 EDTA | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 | 0.1 |
| Purified water | q.s. | q.s. | | | | | | |

- ular, labeled and calibrated 150 milliliter (mL) beakers were each filled with about 90 mL of purified water. **boric acid**, **sodium borate** and mannitol or glycerin were then added and dissolved by stirring the solution for about 25 minutes. At this time, disodium EDTA (ethylene diamine **tetraacetic** acid) was added with stirring. Purified water was added to bring the solutions almost to 100% (100 mL), pH was adjusted to approximately 7.4 and the osmolality was measured. Polyquad.RTM. was then added and the volume brought to 100% by the addition of purified water. pH was again measured and adjusted, if necessary, and the osmolality was measured again.

It is not always necessary to have an isotonic solution; however, if there is a need to have an isotonic solution, the osmolality can be adjusted by incorporating polyol with OH groups in trans position, **sodium chloride**, **potassium chloride**, calcium chloride or other osmolality building

-

Preparation:

Formulations 1-9 were prepared as follows. A first solution (Solution A) was prepared by adding 500 mL of warm purified water to a calibrated two liter aspirator bottle equipped with a magnetic stirrer. PVA and **hydroxyethyl **cellulose** were then added to Solution A and the contents dispersed by stirring. After dispersal of the **polymers**, a filter assembly was attached to the aspirator bottle (142 mm Millipore filter holder with 0.2 filter), and this whole apparatus autoclaved at 121.degree. C. for 30 minutes. Solution A with the filter assembly attached was then allowed to cool to room temperature with stirring. A second solution (Solution B), was prepared in a 500 mL beaker containing 300 mL of purified water by adding **boric acid**, **sodium borate** and mannitol and dissolving the contents by stirring for 25 minutes. Edetate disodium, **sodium chloride**,

---------- 5281277
classes:1 134/18 1 134/30 1 134/42 1 422/26 1 422/28 1 435/188 1 510/114 1 510/393 1 514/839
score: 682

keywords: contact lenses;contact lens;potassium;buffer;lens;aqueous;sodium;chloride;disinfecting;Formulation;dissolving;boric acid;quaternary ammonium;quaternary;polyvinyl;glycerol;organic;skin;sorbitol;potassium;buffer;Lens;disinfecting;lenses;Inventors;enzymatic;aqueous;sodium;chloride;alcohol;acid;liquid;methyl;hydrogen;ammonium;ether;above-mentioned;mixing;boric;borate;adjust;whereupon;

- lizing an enzyme by adding at least 5% of **sorbitol** and at least about 20% of the weight of this **sorbitol**, of borax. However, by the combination of **sorbitol** and borax, no adequate enzyme stability can be attained, and the compatibility with a surfactant is poor, whereby if a surfactant is added at a high concentration, separation is likely to occur.

On the other hand, as a treating solution for contact lenses, Japanese Unexamined Patent Publication No. 167726/1989 discloses a preserving solution having an enzyme incorporated together with a **water-soluble** polymer containing **quaternary ammonium** groups and hydroxyl groups. However, this preserving solution had low cleaning effects and was not adequate as a cleaning solution. Further, Japanese Unexamined Patent Publications No. 159822/1988 and No. 180515/1989 propose a method for stabilizing a protease by incorporating a protease to a solution containing at least 50% of an **organic**

---------- 5919313
classes:1 134/42 1 134/901 1 510/114 1 514/839
score: 679

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;preservatives;ingredient;phosphate;citrate;citric acid;citric;sodium borate;borates;water-soluble;quaternary ammonium;quaternary;copolymers;polyethylene;propylene;glycerol;inorganic;organic;formulated;sorbitol;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;NaCl;disinfect;enzymatic;biguanides;hexamethylene;biguanide;aqueous;compounds;sodium;chloride;acid;liquid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;ppm;mixing;acids;toxicity;efficacy;borate;adjust;comfort;correspond;

- ic
antimicrobial agents used herein are preferably employed in the absence of mercury-containing compounds such as thimerosal. The salts of alexidine and chlorhexidine can be either **organic** or **inorganic** and are typically gluconates, nitrates, **acetates**, phosphates, sulphates, halides and the like.

Particularly preferred are polymeric **quaternary ammonium** compounds of the structure:
##STR2##
wherein: R.sub.1 and R.sub.2 can be the same or different and are selected from:

N.sup.+ (CH.sub.2 CH.sub.2 OH).sub.3 X, N(CH.sub.3).sub.2 or OH;
X is a pharmaceutically acceptable anion, preferably chloride; and
n=integer from 1 to 50.

The most preferred compounds of this structure is polyquaternium-1, which is also known Onamer M.RTM. (registered trademark of Onyx Chemical Corporation) or as Polyquad.RTM. (registered trademark of Alcon Laboratories, Inc.).

The above-described antimicrobial agents are utilized in the methods of the pres
- o the above-described antimicrobial agents, such as suitable **buffer**ing agents, chelating and/or sequestering agents and tonicity adjusting agents. The disinfecting solutions may also contain surfactants.

The tonicity adjusting agents, which may be a component of the disinfecting solution and may optionally be incorporated into the liquid enzyme composition, are utilized to adjust the osmotic value of the final cleaning and disinfecting solution to more closely resemble physiological tonicity. Suitable tonicity adjusting agents include, but are not limited to, sodium and **potassium chloride**, dextrose, and the **buffer**ing agents listed above are individually used in amounts ranging from about 0.01 to 2.5% w/v and preferably, from about 0.5 to about 1.5% w/v.

Suitable surfactants can be either cationic, anionic, nonionic or amphoteric. Preferred surfactants are neutral or nonionic surfactants which may be present in amounts up to 5% w/v.

---------- 5672213
classes:1 134/42 1 134/901 1 435/188 1 510/114 1 514/839
score: 675

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;preservatives;ingredient;phosphate;citrate;citric acid;citric;sodium borate;borates;water-soluble;quaternary ammonium;quaternary;copolymers;polyethylene;propylene;glycerol;inorganic;organic;formulated;sorbitol;potassium;sodium chloride;bu

ffer;Lens;disinfecting;lenses;tonicity;antimicrobial;NaCl;disinfect;enzymatic;biguanides;hexamethylene;bi
guanide;aqueous;compounds;sodium;chloride;acid;liquid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ethe
r;ppm;mixing;acids;toxicity;efficacy;borate;adjust;comfort;correspond;

- o utilize osmolality measurements
to define acceptable tonicity ranges for disinfecting solutions. As indicated above, the antimicrobial activity of disinfecting agents, particularly polymeric **quaternary ammonium** compounds such as polyquaternium-1, is adversely affected by high concentrations of sodium chloride or other ionic solutions.

The ionic strength or tonicity of the cleaning and disinfecting solution of the present invention has been found to be an important factor. More specifically, polymeric ammonium compounds, and particularly those of Formula (I), below, lose antimicrobial activity when the concentration of ionic solutes in the disinfecting solution is increased. The use of solutions having low ionic strengths (i.e., low concentrations of ionic solutes such as **sodium chloride**) is therefore preferred. Such low ionic strengths generally correspond to osmolalities in the range of hypotonic to isotonic, and more

---------- 6165415
classes:1 422/28 1 222/1451 1 422/30 1 422/256 1 422/292 1 514/839 1 514/840
score: 668

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antim
icrobial;aqueous;sodium;chloride;disinfecting;disinfect;disodium;rinse;phosphate;bicarbonate;citric;hydro
xyethyl;polyvinyl alcohol;polyvinyl;polyethylene;propylene glycol;propylene;glycerol;inorganic;EDTA;potas
sium;sodium chloride;viscosity;buffer;Peter;Lens;disinfecting;lenses;tonicity;antimicrobial;disinfect;enz
ymatic;isotonic;hexamethylene;buffers;aqueous;sodium;chloride;alcohol;liquid;glycol;Mixtures;hydrogen;bor
ate;disinfectants;

- m, the contact lens being treated
or the wearer of the treated contact lens. Examples of useful preservative components include, but are not limited to, poly[dimethylimino-2-butene-1,4-diyl]chloride, alpha-[4-tris(2-hydroethyl)ammonium-dichloride (available from Onyx Corporation under the trademark Polyquarternium 1.RTM.), benzalkonium halides such as benzalkonium chloride, alexidine salts, chlorhexidine salts, hexamethylene biguanimides and their **polymers**, and the like and mixtures thereof.

The amount of preservative component included in the second liquid medium varies over a relatively wide range depending, for example, on the specific preservative component being employed. Preferably, the amount of preservative component is in the range of about 0.000001% to about 0.001% or more (.sup.w /.sub.v).

The liquid media, e.g., aqueous liquid media, employed preferably include a **buffer** component which is present in an amount

-
about 200 to about 350 or about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the combined liquid medium substantially corresponds to the tonicity of the fluids of the eye, in particularly the human eye.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the combined liquid medium and do not have deleterious or toxic properties which could harm the eye. Examples of useful tonicity components include **sodium chloride**, **potassium chloride**, mannitol, dextrose, glycerin, **propylene glycol** and mixtures thereof. In one embodiment, the tonicity component is selected from **inorganic** salts and mixtures thereof.

The amount of ophthalmically acceptable tonicity component utilized can vary widely. In one embodiment, the tonicity component is preferably present in the combined li

---------- 5096607
classes:1 422/28 1 510/114
score: 662

keywords: contact lenses;contact lens;potassium;sodium chloride;lens;tonicity;antimicrobial;aqueous;compo
unds;sodium;chloride;disinfecting;disinfect;dissolving;powder;citric acid;citric;borates;polymers;water-s

oluble;ammonium salts;quaternary ammonium;quaternary;polyvinyl;copolymers;polyethylene;inorganic;organic;
severe;potassium;sodium chloride;Lens;disinfecting;lenses;tonicity;antimicrobial;disinfect;inserting;inse
rtion;isotonic;biguanides;hexamethylene;polyaminopropyl;biguanide;aqueous;compounds;sodium;chloride;acid;
liquid;glycol;hydrogen;salts;ammonium;salt;above-mentioned;ppm;mixing;acids;efficacy;citrates;boric;adjus
t;studies;

- ch as poly[(dimethyliminio)-2-butene-1,4-diyl chloride],
[4-tris(2-hydroxyethyl)
ammonio]-2-butenyl-w-[tris(2-hydroxyethyl)ammonio]dichloride (chemical
registry number 75345-27-6) generally available as polyquaternium 1.RTM.
from ONYX Corporation, benzalkonium halides, and biguanides such as salts
of alexidine, alexidine free base, salts of chlorhexidine, hexamethylene
biguanides and their **polymers**. The antimicrobial agents used herein are
preferrably employed in the absence of mercury-containing compounds such
as thimerosal. The salts of alexidine and chlorhexidine can be either
**organic** or **inorganic** and are typically gluconates, nitrates, **acetates**,
phosphates, sulphates, halides and the like. Preferred antimicrobial
agents are the polymeric **quaternary ammonium** salts used in ophthalmic
applications and the biguanides. More preferred are the biguanides with
hexamethylene biguanides, their **polymers** and **water-soluble** salts b

---------- 6319464
classes:1 422/28 1 422/1 1 422/5 1 424/7804 1 514/839 1 514/840
score: 661

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antim
icrobial;aqueous;compounds;sodium;chloride;disinfecting;disinfect;disodium;Formulation;dissolving;preserv
atives;ingredient;citrate;boric acid;borates;quaternary ammonium;quaternary;methyl cellulose;cellulose;su
gar;propylene glycol;propylene;formulated;severe;sorbitol;EDTA;potassium;sodium chloride;viscosity;buffer
;Lens;disinfecting;lenses;Inventors;tonicity;antimicrobial;disinfect;mannitol;biguanides;polyhexamethylen
e;aqueous;compounds;sodium;chloride;alcohol;acid;glycol;Mixtures;methyl;salts;ammonium;toxicity;efficacy;
boric;borate;adjust;comfort;storing;

- 0.45

| | | |
|---|---|---|
| **boric acid** | 0.6 | 0.6 |
| Polyquaternium-1 | 0.001 | 0.001 |
| Sodium Citrate | 0.65 | 0.65 |
| **sodium chloride** | 0.1 | 0.1 |
| **sorbitol** | 1.2 | 1.2 |
| Tetronic 1304 | 0.05 | 0.05 |
| Disodium EDTA | 0.05 | -- |
| NaOH/HCl | pH 7.8 | pH 7.8 |
| Purified Water | QS | QS |

The anti-microbial activity of the above compositions against P.
aeruginosa, S. marcescens, S. aureus, and C. albicans was evaluated using
a protocol similar to that of Example 1, above. The log reduction data is
illustrated in Table 5, below:

TABLE 5

| Microorganism | Time (Hrs) | Formulation E | Formulation F |
|---|---|---|---|
| P. aeruginosa | 6 | 4.7 | 4.7 |
| ATCC 9027 | 24 | 6.0 | 6.0 |

---------- 4758595
classes:1 424/7826 1 424/7808 1 514/635
score: 647

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antim
icrobial;PHMB;aqueous;compounds;sodium;chloride;disinfecting;disodium;Formulation;dissolving;preservative
s;ingredient;phosphate;sodium bicarbonate;bicarbonate;citrate;citric;sodium borate;boric acid;water-solub
le salt;polymers;water-soluble;quaternary ammonium;quaternary;hydroxyethyl;cellulose;polyvinyl alcohol;po
lyvinyl;polyethylene;propylene glycol;propylene;glycerol;organic;formulated;EDTA;potassium;sodium chlorid
e;viscosity;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;PHMB;isotonic;poloxamer;miranol;biguan
ides;hexamethylene;biguanide;polyhexamethylene;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;gly
col;Mixtures;methyl;hydrogen;salts;ammonium;salt;ppm;toxicity;boric;borate;comfort;cytotoxic;disinfectant
s;

- on, MC Publishing Co., Glen Rock, NJ 07452.
It may also be desirable to include **water-soluble viscosity** builders in the

PHMB-containing solutions of the present invention. Because of their demulcent effect, **viscosity** buildiers have a tendency to enhance the lens wearer's comfort by means of a film on the lens surface cushioning impact against the eye. Included among the **water-soluble viscosity** builders are the **cellulose polymers** like **hydroxyethyl** or hydroxypropyl **cellulose**, carboxymethyl **cellulose** and the like. Such **viscosity** builders may be employed in amounts ranging from about 0.01 to about 4.0 weight percent or less.

This invention relates to disinfecting and/or preserving solutions for use with most contact lenses, including hard and soft lenses, as well as the newer hard gas permeable type contact lenses, such as described in U.S. Pat. No. 4,327,203. The term "soft contact lens" as used herein generally refers to those c

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---------- 5718895
classes:1 424/941 1 422/28 1 424/943 1 424/464 1 435/264
score: 645

keywords: contact lenses;contact lens;potassium;sodium chloride;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;preservatives;ingredient;phosphate;TRIS;citrate;citric acid;citric;borates;organic acids;polymers;water-soluble;quaternary ammonium;quaternary;Pluronic;copolymers;polyethylene;propylene;inorganic;organic;formulated;sorbitol;potassium;sodium chloride;Lens;disinfecting;lenses;tonicity;antimicrobial;NaCl;disinfect;enzymatic;biguanides;hexamethylene;biguanide;aqueous;compounds;sodium;chloride;alcohol;acid;liquid;glycol;Mixtures;hydrogen;salts;ammonium;ether;salt;acids;toxicity;efficacy;boric;borate;adjust;correspond;disinfectants;

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- yed to purify the mutant type enzymes exhibiting low pIs. Enzymes with lysine residues replaced with lower pI amino acids are preferred modified enzymes of this class of modified enzymes of the present invention.

The enzymes of the present invention may be selected from those that have been chemically modified, covalently, with **organic** monomer or polymer molecules. As used herein, "organic monomer covalent linkage" refers to the linking of small **organic** monomers covalently to an enzyme; and "organic polymer covalent linkage" refers to linking large **organic** **polymers** covalently to an enzyme. Examples of **organic** monomers include succinate, and methyl, ethyl or proplyl acylates. Examples of **organic** **polymers** include various **polyethylene** glycols (PEG), such as PEG 500, 1000 and 2000. Such modifications have been discused in U.S. Pat. No. 5,122,614, the entire contents of which are incorporated herein by reference. The use of th

- blet when enzyme tablets are employed.

Examples of suitable **buffer**ing agents which may be incorporated into an enzyme tablet include, but are not limited to, alkali metal salts such as **potassium** or sodium carbonates, **acetates**, **borates**, phosphates and citrates, and weak acids such as acetic and **boric acid**s. Preferred **buffer**ing agents are alkali metal **borates** such as sodium or **potassium** **borates**. Additionally, other pH adjusting agents may be employed such as **inorganic** or **organic acids** and bases. For example, hydrochloric acid, sodium hydroxide, triethanolamine or Tris may be employed in concentrations suitable for ophthalmic uses. Generally, **buffer**ing agents are present in amounts from about 0.01 to about 2.5% (w/v) and preferably, from about 0.5 to about 1.5% (w/v), of the working solution.

Effervescing agents are typically employed when the enzyme is provided in solid form. Examples of suitable effervescing agents include, but are

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---------- 5811466
classes:1 424/660 1 134/901 1 422/28 1 514/635 1 514/839
score: 626

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;viscosity;buffer;lens;antimicrobial;aqueous;compounds;sodium;chloride;disinfecting;disodium;Formulation;dissolving;preservatives;ingredient;gels;phosphate;citrate;citric acid;citric;sodium borate;boric acid;polymers;water-soluble;quaternary ammonium;quaternary;tetraacetic;hydroxyethyl cellulose;hydroxyethyl;cellulose;polyvinyl;Pluronic;sugar;propylene glycol;propylene;organic;formulated;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;antimicrobial;isotonic;mannitol;biguanides;biguanide;polyhexamethylene;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;glycol;Mixtures;salts;ammonium;mixing;acids;efficacy;boric;borate;comfort;gas-permeable;disinfectants;

---

- 0.35

0.35
0.35
0.35
0.35
0.35
0.35
0.35
0.5

**sodium borate**
0.11
0.11
0.11
0.11
0.11
0.11
0.11
-- --

**sodium chloride**
0.45
0.45
0.45
-- 0.45
0.45
0.45
0.45
-- --

Edetate disodium
0.1
0.1
0.1
0.1

- lyquad.RTM. were added, with stirring. The second solution was then added to the first solution via a 0.2.mu. filter. Last, the pH was adjusted to 7.4 and the volume brought to 100% with purified water.

EXAMPLE 5

The following is a typical daily cleaner composition of the present invention for use with RGPs and may be prepared in a manner similar to that detailed in Example 4.

| INGREDIENT | AMOUNT (wt %) |
|---|---|
| Nylon 11 | 2.50 |
| Dextran 70 | 6.0 |
| **sodium borate** | 0.25 |
| **boric acid** | 0.50 |
| Miracare .RTM. 2MCA | 0.50 |
| PDMA-1 | 0.15 |
| **propylene glycol** | 10.0 |
| Polyquad .RTM. | 0.0055 |
| EDTA | 0.10 |
| Mannitol | 1.20 |
| NaOH and/or HCl | pH 7.4 |
| Purified water | q.s. |

EXAMPLE 6

The following is a typical wetting and soaking composition of the

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---------- 4285738
classes:1 134/26 1 134/28 1 134/42 1 510/112 1 510/114 1 510/392 1 510/421 1 510/490 1 510/492 1 510/499 1 510/501
score: 599

keywords: contact lenses;contact lens;sodium chloride;lens;aqueous;compounds;sodium;chloride;disodium;phosphate;water-soluble;cellulose;urea;organic;sodium chloride;Lens;lenses;lachrymal;aqueous;compounds;sodium;chloride;acid;methyl;salts;ether;salt;above-mentioned;acids;kinds;

- c enzyme is 0.005 (W/V)% or more, but even if it is 0.001 (W/V)% or less, satisfactory results will certainly be obtained by prolonged treatment. A 20 (W/V)% urea solution or a solution containing the proteolytic enzyme alone does not provide satisfactory results within 6 hours.

Table 3 shows the relative durations of time required for removal of proteinaceous matter artificially deposited on each of contact lenses, by using each of 0.5 (W/V)% proteolytic enzyme solution containing a sulfhydryl compound, for example 1 (W/V)% of sodium hydrosulfite, and 0.9 (W/V)% of **sodium chloride**, with or without addition of 20 to 35 (W/V)% of urea, adjusted to pH 7.0 with 1 N-sodium hydroxide.

TABLE 3

| Enzyme | Concentration of urea | Time required for removal of proteinaceous matter |
|---|---|---|
| - | 20 | ++ |

As clearly shown in Table 4, the cleaning effect appears markedly by addition of urea even in a concentration of a proteolytic enzyme which shows almost no cleaning effect in the absence of urea.

Thus, the combined use of a proteolytic enzyme and urea and/or an acid salt of guanidine provides an excellent synergistic effect in the presence of a sulfhydryl compound.

Depending on the cleaning composition used, soft contact lenses may be slightly swollen. However, when allowed to stand in physiological saline solution, they regain the original shapes, and their physical properties are not affected.

It is to be noted that the present invention may also be applied to hard contact and silicone contact lenses.

A **buffer**, chelating agent, etc. may be incorporated in the cleaning composition in accordance with the present invention.

The present invention will now be described in detail by way

- sodium monohydrogen phosphate and 50 mg of proteinase, followed by addition of a sufficient amount of water to make 10 ml. A soft contact lens used for 3 months and contaminated with proteinaceous matter was allowed to stand in this solution for about 15 minutes and thereafter treated as in Example 1. By the above procedure, there was obtained a cleaned lens.

EXAMPLE 8

A plastic container was filled with 3.5 g of guanidine hydrochloride, 90 mg of sodium hydrogensulfite, 60 mg of sodium sulfite, 10 mg of sodium edetate, 0.1 g of **sodium chloride** and 50 mg of protease, followed by addition of a sufficient amount of water to make 10 ml. A soft contact lens contaminated with proteinaceous matter was allowed to stand in this solution for about 15 minutes, and thereafter treated as in Example 1. By the above procedure, there was obtained a cleaned lens.

EXAMPLE 9

A plastic container was filled with 2.0 g of urea, 0.1 g of cysteine

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---------- 6069120
classes:1 510/114 1 514/839 1 514/840
score: 595

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;preservatives;ingredient;phosphate;citrate;citric acid;citric;boric acid;water-soluble;quaternary ammonium;quaternary;copolymers;polyethylene;propylene;glycerol;inorganic;organic;formulated;sorbitol;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;NaCl;disinfect;enzymatic;biguanides;hexamethylene;biguanide;aqueous;compounds;sodium;chloride;acid;liquid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;ppm;mixing;acids;toxicity;efficacy;boric;borate;adjust;comfort;correspond;

- -described antimicrobial agents, such as suitable **buffer**ing agents, chelating and/or sequestering agents and tonicity adjusting agents. The disinfecting solutions may also contain surfactants.

The tonicity adjusting agents, which may be a component of the disinfecting solution and may optionally be incorporated into the liquid enzyme composition, are utilized to adjust the osmotic value of the final cleaning and disinfecting solution to more closely resemble that of human.

Suitable tonicity adjusting agents include, but are not limited to, sodium and **potassium chloride**, dextrose, calcium and magnesium chloride, the **buffer**ing agents listed above are individually used in amounts ranging from about 0.01 to 2.5% w/v and preferably, from about 0.5 to about 1.5% w/v.

Suitable surfactants can be either cationic, anionic, nonionic or amphoteric. Preferred surfactants are neutral or nonionic surfactants which may be present in amounts

- up to 5% w/v. Examples of suitable surfactants include, but are not limited to, **polyethylene** glycol esters of fatty acids, polyoxyethylene ethers of C.sub.12 -C.sub.18 alkanes and polyoxyethylene-polyoxypropylene block **copolymers** of ethylene diamine (i.e. poloxamine).

Examples of preferred chelating agents include **ethylenediamine**tetraacetic acid (EDTA) and its salts (e.g., disodium) which are normally employed in amounts from about 0.025 to about 2.0% w/v.

The methods of the present invention will typically involve adding a small amount of a liquid enzyme composition of the present invention to about 2 to 10 mL of disinfecting solution, placing the soiled lens into the enzyme/disinfectant solution, and soaking the lens for a period of time effective to clean and disinfect the lens. The small amount of liquid enzyme composition can range due to various applications and the amount of disinfecting solution used, but generally it

- with sodium hydroxide. The enzyme was then added and the volume adjusted to 100% with purified water. The optimal pH of the above formulation is in the range of 6-8, a pH of 7.5 is most preferred.

B. Disinfecting Solution

The following formulation represents a preferred disinfecting solution:

| Ingredient | w/v (%) |
|---|---|
| Polyquaternium-1 | 0.001 + 10% excess |
| **sodium chloride** | 0.48 |
| Disodium Edetate | 0.05 |
| **citric** acid monohydrate | 0.021 |
| Sodium citrate dihydrate | 0.56 |
| Purified water | QS |

To prepare the above formulation, sodium citrate dihydrate, **citric** acid monohydrate, disodium edetate, **sodium chloride** and polyquaternium-1, in the relative concentrations indicated above, were mixed with purified water and the components allowed to dissolve by stirri

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---------- 6228323
classes:1 422/28 1 424/941 1 424/943 1 435/264
score: 581

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;tonicity;PHMB;aqueous;compoun ds;sodium;chloride;disinfecting;disinfect;disodium;Formulation;preservatives;ingredient;powder;phosphate; sodium bicarbonate;bicarbonate;citrate;citric acid;citric;sodium borate;boric acid;water-soluble;quaterna ry ammonium;quaternary;cellulose;Pluronic;polyethylene;propylene glycol;propylene;glycerol;inorganic;orga nic;formulated;sorbitol;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;tonicity;PHMB;disinfect ;inserting;enzymatic;mannitol;poloxamer;biguanides;biguanide;polyhexamethylene;aqueous;compounds;sodium;c hloride;acid;liquid;glycol;methyl;hydrogen;salts;ammonium;mixing;acids;efficacy;boric;borate;adjust;studi es;gas-permeable;disinfectants;store;storing;

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- ution, following dispersion of a Part I Al-trypsin composition in a Part II composition. A final concentration of about 5-25 PAU/mL is preferred. For purposes of this specification, a "proteolytic activity unit" or "PAU" is defined as the amount of enzyme activity necessary to generate one microgram (mcg) of tyrosine per minute ("mcg Tyr/min"), as determined by the casein-digestion, colorimetric assay described below.

Casein-Digestion Assay

A 5.0 mL portion of casein substrate (0.65% casein w/v) is equilibrated for 10 minutes (min) .+-.5 seconds (sec) at 37.degree. C. An enzyme solution is prepared from a Part I enzyme composition by solubilizing and diluting the Part I composition in PBS **buffer**. A 1.0 mL portion of this enzyme solution (0.2 mg/ml) is then added to the casein substrate and the mixture

vortexed, then incubated for 10 min .+-.5 sec at 37.degree. C. After incubation, 5.0 mL of 14% trichloroacetic acid is added an

- NaCl, **sugar**s), a chelating agent (e.g., EDTA), and surfactants (e.g., block **copolymers**). Other agents which enhance the anti-microbial efficacy of the compositions, such as amino alcohols and alkylamines, may also be added. Preferred Part II compositions comprise polyquaternium-1, **sodium borate**, **boric acid**, **propylene glycol** and **Pluronic** P-103. The most preferred Part II compositions comprise **boric acid**, **sorbitol**, 95% 2-amino-2-methyl-1-propanol ("AMP-95"), sodium citrate, **sodium chloride**, disodium edetate, polyquaternium-1, poloxamer 1304 ("Tetronic 1304") and myristamidopropyl diamethyl amine ("MAPDA").

The multi-purpose compositions are intended to be used with various types of contact lenses including rigid gas-permeable ("RGP") lenses and soft lenses.

The cleaning obtained with the liquid enzyme compositions of the present invention is a function of the time. The soaking times utilized will generally vary from about 1 hour

- I

Al-trypsin composition will be added to about 120 mL of a Part II composition, although greater or lesser amounts are contemplated by the present invention.

The Part I Al-trypsin compositions of the present invention will demonstrate effective cleaning efficacy while exhibiting minimal adverse effects or, more preferably, enhanced effects on the anti-microbial activity of anti-microbial agents. The anti-microbial activity of disinfecting agents, particularly polymeric **quaternary ammonium** compounds such as polyquaternium-1, is adversely affected by high concentrations of **sodium chloride** or other ionic solutes. More specifically, polymeric **quaternary ammonium** compounds, and particularly those of Formula (I), below, lose anti-microbial activity when the concentration of ionic solutes in the multi-purpose compositions is too high. Generally, the multi-purpose compositions of the present invention will have tonicities/o

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---------- 6503497
classes:1 424/7804 1 424/427 1 514/912 1 514/839 1 514/840
score: 576

keywords: contact lenses;contact lens;EDTA;potassium chloride;potassium;sodium chloride;viscosity;buffer;lens;antimicrobial;aqueous;compounds;sodium;chloride;disinfecting;disodium;Formulation;dissolving;preservatives;ingredient;gels;phosphate;citrate;citric acid;citric;sodium borate;boric acid;polymers;water-soluble;quaternary ammonium;quaternary;tetraacetic;hydroxyethyl cellulose;hydroxyethyl;cellulose;polyvinyl;Pluronic;sugar;propylene glycol;propylene;organic;formulated;sorbitol;EDTA;potassium chloride;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;antimicrobial;isotonic;mannitol;biguanides;polyhexamethylene;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;glycol;Mixtures;salts;ammonium;mixing;acids;efficacy;boric;borate;comfort;gas-permeable;disinfectants;

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- issolved by stirring the solution for about 25 minutes. At this time, disodium EDTA (ethylene diamine **tetraacetic** acid) was added with stirring. Purified water was added to bring the solutions almost to 100% (100 mL), pH was adjusted to approximately 7.4 and the osmolality was measured. Polyquad.RTM. was then added and the volume brought to 100% by the addition of purified water. pH was again measured and adjusted, if necessary, and the osmolality was measured again.

It is not always necessary to have an isotonic solution; however, if there is a need to have an isotonic solution, the osmolality can be adjusted by incorporating polyol with OH groups in trans position, **sodium chloride**, **potassium chloride**, calcium chloride or other osmolality building agents which are generally acceptable in ophthalmic formulations and known to those skilled in the art.

EXAMPLE 2

Aqueous ophthalmic compositions of the present invention may be prepared

- ater to a calibrated two liter aspirator bottle equipped with a magnetic stirrer. PVA and **hydroxyethyl **cellulose** were then added to Solution A and the contents dispersed by stirring. After dispersal of the **polymers**, a filter assembly was attached to the aspirator bottle (142 mm Millipore filter holder with 0.2 i filter), and this whole apparatus autoclaved at 121.degree. C. for 30 minutes. Solution A with the filter assembly attached was then allowed to cool to room temperature with stirring. A second solution (Solution B), was prepared in a 500 mL beaker containing 300 mL of purified water by adding **boric acid**, **sodium borate** and mannitol and dissolving the contents

by stirring for 25 minutes. Edetate disodium, **sodium chloride**, preservatives and other osmolality-building agents, as necessary, were added to Solution B and the contents dissolved with stirring. Solution B was then sterile filtered into the aspirator bottle c

---------- 6482799
classes:1 514/14 1 422/28 1 424/405 1 514/15 1 530/327 1 530/328
score: 567

keywords: contact lenses;contact lens;constituent;EDTA;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antimicrobial;aqueous;substances;compounds;sodium;chloride;NaCl;disinfecting;disinfect;disodium;Formulation;dissolving;preservatives;powder;phosphate;TRIS;bicarbonate;citrate;sodium borate;boric acid;borates;quaternary;hydroxyethyl;cellulose;polyvinyl;Pluronic;copolymers;polyethylene;propylene glycol;propylene;inorganic;organic;formulated;severe;skin;constituent;EDTA;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;Inventors;tonicity;antimicrobial;NaCl;disinfect;medicinal;insertion;dryness;enzymatic;variable;isotonic;poloxamer;buffers;aqueous;substances;compounds;sodium;chloride;acid;liquid;fluid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;salt;mixing;acids;toxicity;efficacy;drying;boric;borate;adjust;studies;kinds;disinfectants;storing;

- 10 mM SP was stable exhibiting a time-dependent kill with a 6 log kill after a 60 minute exposure (FIG. 3). Frozen L-indolicidin in 10 mM SP with NaCl was stable exhibiting a dose dependent kill with about 1.5 log kill after a 4 hour exposure (FIG. 4).

These data show that L-indolicidin is stable over a period of 14 days in 10 mM SP with and without 0.85% NaCl. However, the presence of NaCl reduces the antimicrobial activity of L-IND and the frozen samples exhibit higher antimicrobial activity compared to the samples that were tested immediately after removal from the commercial containers.

B) Long-term Stability Study of L-Indolicidin

Long term stability of indolicidin was evaluated in a commercial container (Rite-Aid). The L-indolicidin concentration was 50 .mu.g/ml **formulated** in a 10 mM sodium phosphate **buffer**, pH 7.4, with and without 0.85% sodium chloride. The test organism was S. aureus ATCC 6538. Sampling time was 0, 1, 2, 3

- /ml .mu.g/ml .mu.g/ml .mu.g/ml .mu.g/ml

| | | | | | | |
|---|---|---|---|---|---|---|
| 0.85% NaCl | 1 | 1.5 | 1 | <1 | 0 | 0 |
| 0.2% EDTA | 5 | 5 | 5 | 5 | 5 | 5 |
| 0.5% Pluromc | 0 | 0 | 0 | 0 | 0 | 0 |
| Tris only | 0 | 0 | 0 | 0 | 4 | 4 |

TABLE 14

Log kill of P. aeruginosa exposed to 8 and 32 .mu.g/ml L-indolicidin in three concentrations of Tris **buffer** without (Tris only), or with various additives (second test).

| | 1 mM Tris | | 5 mM Tris | | 10 mM Tris | |
|---|---|---|---|---|---|---|
| Additive | 8 | 32 | 8 | 32 | 8 | 32 |
| (wt %) | .mu.g/ml | .mu.g/ml | .mu.g/ml | .mu.g/ml | .mu.g/ml | .mu.g/ml |
| 0.85% NaCl | 0 | 1 | 0 | 3 | NA | NA |
| 0.2% EDTA | 5 | 5 | 5 | 5 | 5 | 5 |
| 0.5% **Pluronic** | 0 | 0 | 0 | 0 | 0 | 0 |
| Tris only | 0 | 0 | 0 | 0 | 4 | 4 |

NA: Data not available, plating error.

Log ki

---------- 5011661
classes:1 422/30 1 134/27 1 422/28 1 422/292 1 422/293 1 424/471 1 424/482 1 514/840
score: 564

keywords: contact lenses;contact lens;potassium;sodium chloride;buffer;lens;antimicrobial;aqueous;substances;sodium;chloride;disinfecting;disinfect;disodium;dissolving;heavy;powder;phosphate;citrate;polymers;water-soluble;cellulose;polyvinyl alcohol;polyvinyl;copolymers;polyethylene;organic;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;antimicrobial;disinfect;enzymatic;mannitol;aqueous;substances;sodium;chloride;alcohol;acid;glycol;methyl;hydrogen;salts;ether;mixing;borate;adjust;comfort;correspond;

- oncentrate, 260,000 units/mL

0.05 weight percent hydroxypropylmethylcellose USP XX
0.05 weight percent NaH.sub.2 PO.sub.4 .times.2H.sub.2 O DAB 8
0.25 weight percent Na.sub.2 HPO.sub.4 .times.2H.sub.2 O
0.75 weight percent **sodium chloride** EP I
The following is a further suitable composition of the neutralizing agent:

3-12 mg suitable **buffer** substance(s) or mixture, for example, alkali phosphate, borate or citrate, glycine
40-70 mg neutral electrolyte (for example, NaCl, KCl)
5-10 mg alkali hydrogen carbonate
5-10 mg **water-soluble** polymer, for example, **polyvinyl**pyrrolidone
0.2-1 mg catalyst (catalase, peroxidase)
per single dose.
This amount is sufficient to decompose, to neutralize and to adjust to an osmolarity of 270-320 mosmol 7 mL of an hydrogen peroxide solution. These 7 mL correspond to the volume of a standard contact lens case or contact lens treatment body.
An example of a further special composition of the neutralizing agent is the following:
5.6 mg p
- roxyethylcellulose, hydroxypropylcellulose, **hydroxyethyl**cellulose, sodium carboxymethylcelluloses; **cellulose** acetate phthalate; hydroxypropylmethylmethylcellulose phthalate; **polymers** of methacrylic acid and methacrylate esters; a coating of an aqueous dispersion of a copolymer of methacrylic acid and methacrylate esters; a coating of an aqueous dispersion of **cellulose** acetate phthalate; **copolymers** of methyl vinyl ether and maleic anhydride and **polyvinyl** alcohols.

Suitable polyalcohols, especially in an amount of 0.2-1 mg/tablet, can be added to these **polymers** to control the time delay, 1,2-propyleneglycol **polyethylene** glycols and citrate esters being suitable as polyalcohols.
The coating can be produced from the **water-soluble** polymer by known processes, for example, by spray-coating a film in the coating pan, by the fluidized bed process (Wurster process) or in closed systems. The preferred amount of polymer, coating a tablet,

---------- 6274133
classes:1 424/7804 1 514/781 1 514/912
score: 547

keywords: contact lenses;contact lens;potassium chloride;potassium;sodium chloride;viscosity;buffer;lens;tonicity;antimicrobial;aqueous;substances;compounds;sodium;chloride;disinfecting;disodium;Formulation;ingredient;heavy;phosphate;citric;sodium borate;boric acid;polymers;water-soluble;ammonium salts;quaternary ammonium;quaternary;hydroxyethyl cellulose;hydroxyethyl;cellulose;polyvinyl;polyethylene;propylene glycol;propylene;glycerol;inorganic;organic;potassium chloride;potassium;sodium chloride;viscosity;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;lachrymal;insertion;isotonic;poloxamer;biguanides;hexamethylene;polyaminopropyl;biguanide;polyhexamethylene;buffers;aqueous;substances;compounds;sodium;chloride;acid;prevents;fluid;glycol;Mixtures;methyl;salts;ammonium;ether;salt;mixing;efficacy;boric;borate;adjust;comfort;gas-permeable;

- on, NV Division, 3000 Continental, Mount Olive, N.J. 07628-1234, USA). In the present compositions, the PVP is suitably present in an amount 0.01 to 10.0% by weight, preferably of between 0.05 to 5.0 percent by weight.

The present composition will contain a disinfecting amount of a preservative or an antimicrobial agent. A particularly preferred preservative is sorbic acid (0.15%). Antimicrobial agents are defined as **organic** chemicals which derive their antimicrobial activity through a chemical or physiochemical interaction with the microbial organisms. For example, biguanides include the free bases or salts of alexidine, chlorhexidine, hexamethylene biguanides and their **polymers**, and combinations of the foregoing. The salts of alexidine and chlorhexidine can be either **organic** or **inorganic** and are typically gluconates, nitrates, **acetates**, phosphates, sulphates, halides and the like. Other preferred antimicrobial agents ar
- e the polymeric **quaternary ammonium** salts used in ophthalmic applications and the biguanides, for example, the hexamethylene biguanides (commercially available from Zeneca, Wilmington, DE under the trademark Cosmocil.TM. CQ), their **polymers** and **water-soluble** salts. Generally, the hexamethylene biguanide **polymers**, also referred to as polyaminopropyl biguanide (PAPB), have molecular weights of up to about 100,000. Such compounds are known and are disclosed in U.S. Pat. No. 4,758,595 and British Patent 1,432,345, which patents are hereby incorporated herein by reference. The hydrochloride salt of polyhexamethylene biguanide is commercially available from Zeneca, Inc. under the trademark Cosmocil.RTM. CQ. This biguanide is often referred to as either "PHMB" or "PAPB," as herein, usually by the latter acronym corresponding to polyaminopropyl biguanide.

In addition to the active ingredients described above, solutions employed
i

---------- Re32672
classes:1 435/264 1 424/616 1 510/114 1 510/115 1 510/372 1 510/374 1 514/840
score: 534

keywords: contact lenses;contact lens;EDTA;potassium;sodium chloride;buffer;lens;tonicity;antimicrobial;aqueous;compounds;sodium;chloride;disinfecting;disinfect;sodium perborate;perborate;Formulation;dissolving;ingredient;heavy;powder;phosphate;bicarbonate;polymers;water-soluble;sodium salts;polyethylene;organic;formulated;sorbitol;EDTA;potassium;sodium chloride;buffer;Lens;disinfecting;lenses;tonicity;antimicrobial;disinfect;inserting;enzymatic;buffers;aqueous;compounds;sodium;chloride;acid;fluid;glycol;hydrogen;salts;acids;efficacy;borate;adjust;comfort;studies;microbiological;disinfectants;soak;storing;

- 0% 20% 32%

These figures demonstrate that each of the 3% peroxide solutions is a much more effective disinfectant when subtilisin A is present. The effect is particularly pronounced in the A-OSept system.
EXAMPLE 7
Effect of Peroxide Concentration on Enzyme Activity
The enzymatic activity of the subtilisin A tablet described in Example 1 and trypsin was determined at different hydrogen peroxide concentrations using the Modified Azocoll method "Sigma Catalog". Baker Chemical Company, 30% hydrogen peroxide was used. Appropriate dilutions were made with a 0.2M borate **buffer** at about pH 8.4. Azocoll substrate and trypsin were obtained from Sigma Corporation.
Peroxide was first diluted with **buffer** to the appropriate concentrations. One enzyme tablet was dissolved in 10 ml of **buffer** to which had been added 50 mg of Azocoll substrate. One ml of this solution was then added to each of
- n peroxide concentrations
between 2-6%. Table V indicates that trypsin is active in hydrogen peroxide.
EXAMPLE 7
Effects of Perborate on Enzyme Activity
Hydrocurve II.RTM. lenses were coated with heat-denatured lysozyme as per the procedure described in Example 1. The following solutions based on subtilisin A (Novo Industries, Denmark) and sodium perborate were prepared to test the combined effects of perborate as a source of peroxide on the proteolytic activity of subtilisin A. Solution A--0.04 mg/ml subtilisin A, bicarbonate **buffer** to adjust the pH to 8.307; Solution B--0.02% (w/v) sodium perborate, bicarbonate **buffer**, pH adjusted to 8.533; and Solution C--0.04 mg/ml subtilisin A, 0.02% (w/v) sodium perborate, bicarbonate **buffer**, pH adjusted to 8.532. Each treatment was done in a 10 ml volume.
Five protein coated lenses were soaked in each of these solutions (10 ml) for 3 hours at room temperature. All lenses were then rinsed and

---------- 6423323
classes:1 424/401 1 424/7024 1 424/489 1 510/101 1 514/680
score: 370

keywords: panthenol;aqueous;substances;sodium;Formulation;preservatives;propylene glycol;propylene;urea;organic;formulated;skin;aqueous;substances;sodium;alcohol;acid;prevents;glycol;Mixtures;mixing;acids;

- of **propylene glycol**;
from 1.3 to 4.2% by weight of **glycerol**;
from 1 to 3% by weight of cetyl sarcosinate;
from 0.05 to 1% by weight of allantoin; and
water as the balance to make 100% by weight.
In another preferred embodiment, the foam skin cream according to the invention additionally contains a silicone-containing substance, such as dimethicone. This substance is added to phase I. Preferably, it is present in amounts of from 0.05 to 1% by weight.
In addition, the foam skin cream according to the invention may additionally contain one or more refatting substances in phase I, such as decyl oleate, isohexadecane, stearic acid glycol ester, coconut fatty acid ethanolamide, corn oil, peanut oil, almond oil, sesame oil, olive oil, jojoba oil, soybean oil, wool wax alcohols, paraffin, medium-chain triglycerides, oleic acid oleyl esters, white petrolatum,

macrogol-glycerol hydroxystearate, hydrogenated castor oil, castor oil from Ricinus com

- oxic eczema, toxic-irritative eczema, microbial-dysregulative eczema, atopic dermatitis, atopic palmoplantar eczema, dyshidrosis, hyperhidrosis, contact urticaria, intertriginous eczema in connection with hemorrhoids, various weeping fungal infections, e.g., interdigital mycosis, perleches, psoriasis vulgaris, ulcus cruris, cholinergic urticaria, diaper dermatitis.

It may be indicated to include substances which can increase the moisture content of the skin, in addition to refatting substances. Such hydratizing substances include, in particular, urea, ethoxydiglycol, **sodium chloride**, magnesium chloride, **sorbitol**, dexpanthenol, sodium lactate, allantoin, hyaluronic acid, vitamin E, linolenic acid. The amount of those substances can be from 1 to 20% by weight or more of the respective substances, depending on the severity of the disease to be treated. These quantities also apply, in particular, to urea which may also be present

---------- 5653970
classes:1 424/7024 1 424/701 1 510/126 1 510/135 1 514/847
score: 363

keywords: panthenol;EDTA;potassium;sodium chloride;viscosity;surface-active;antimicrobial;aqueous;substances;compounds;sodium;chloride;disodium;Formulation;rinse;preservatives;ingredient;phosphate;citric acid;citric;sulfonates;polymers;ammonium salts;quaternary ammonium;quaternary;tetraacetic acid;ethylenediamine tetraacetic;tetraacetic;ethylenediamine;polyacrylic;hydroxyethyl;methyl cellulose;cellulose;Pluronic;copolymers;polyethylene;sugar;propylene glycol;propylene;urea;glycerol;inorganic;organic;formulated;cleansing;skin;sorbitol;EDTA;potassium;sodium chloride;viscosity;surface-active;Address;antimicrobial;pantothenic;Provitamin;enzymatic;variable;poloxamer;miranol;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;prevents;fluid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;salt;ppm;mixing;acids;drying;boric;adjust;studies;

- -- -- -- -- --
**cellulose**
32. **polyvinyl**pyrroli-
-- -- 0.7 -- -- -- --
done
33. Talc -- -- 5.0 -- -- -- --
34. Propyltrimonium
5.0 -- -- -- -- -- --
Hydrolyzed Collagen
35. TEA Coco
-- -- -- -- 10.0 -- --
Hydrolyzed Animal
Protein
36. Polyquaternium-10
-- -- -- 2.0 -- -- --
37. Polyquaternium-24
-- 0.3 -- -- -- -- --
38. Aloe Vera Gel
-- -- -- -- 0.5 -- --
39. Allantoin
-- -- -- -- 0.2 -- --
40. **sorbitol** (70%)
-- -- 5.0 -- 1.3 -- --
41. Glycerin
-- 4.0 -- -- -- -- --
42. **propylene glycol**
3.0 -- -- 0.5 -- --
43. Diazolidinyl Urea
0.3 -- -- 0.2 -- -- --
44. Methyl

---------- 3968046
classes:1 510/303 1 252/181 1 510/307 1 510/318 1 510/351 1 510/355 1 510/361 1 510/368 1 510/370 1 510/378 1 510/398 1 510/434 1 510/477 1 510/495 1 510/533 1 562/584 1 562/595
score: 360

keywords: potassium;buffer;g/l;substances;compounds;sodium;perborate;Formulation;heavy;powder;citrate;citric acid;citric;sulfonates;polyacrylic;polyvinyl alcohol;polyvinyl;organic;potassium;buffer;g/l;variable;abbreviated;substances;compounds;sodium;alcohol;acid;liquid;hydrogen;salts;ammonium;ether;salt;above-mentioned;ppm;acids;toxicity;whereupon;disinfectants;

- itions being exactly the same
as in Example 7.

TABLE XIII

| Powder Active material | % of sodium salt of SPC | % of Ca.sup.2.sup.+ in solution |
|---|---|---|
| No. | | |
| 1 6% Tergitol 15 S 9<br>4% LAS<br>3% of tallow fatty acid soap: | 8 | 95.2 |
| 2 8% LAS<br>3% FAS<br>3% tallow fatty acid soap: | 8 | 95.0 |
| 3 8% Tergitol 15 S 9: | 8 | 96.1 |
| 4 6% Tergitol 15 S 9<br>4% FAS<br>3% tallow fatty acid soap: | 8 | 95.6 |
| 5 6% CITREX<br>6% Tergitol 15 S 9: | 5 | 97.9 |
| 6 6% LAS<br>3% FAS<br>4% Tergitol 15 S 9<br>3% tallow fatty acid soap: | | |

---------- 5824629
classes:1 510/120 1 510/119 1 510/125 1 510/127 1 510/135 1 510/140 1 510/141 1 510/142 1 510/148 1 510/1
56 1 510/414 1 510/419 1 510/424 1 510/434 1 510/435 1 510/439 1 510/440 1 510/445 1 510/446 1 510/447 1
510/477 1 510/478 1 510/509
score: 356

keywords: aqueous;substances;compounds;sodium;sodium bicarbonate;bicarbonate;citric;ammonium salts;quater
nary;cellulose;organic;cleansing;skin;motion;aqueous;substances;compounds;sodium;alcohol;acid;liquid;Mixt
ures;methyl;hydrogen;salts;ammonium;ether;mixing;acids;drying;

- nsing effect, however, without ignoring the positive
after-wash regenerating effects.
From the classes of anionic surfactants listed above, the individual
anionic surfactant taken from the group of sodium- or magnesium-lauryl- or
cetyl-sulfate or sulfonate, cocos fatty acid mono- or di-ethanol amide and
(sodium- or magnesium-) cumene sulfate or sulfonate are preferred due to
their beneficial long-term effects extending beyond the **cleansing** process
itself.
If the emphasis of the new solid phase agent is less on a separate
**cleansing** effect and more on hair care--and, of course, also on the
simultaneous scalp and skin care--, then the best solution are surfactants
from the groups of cationic surfactants, such as **quaternary ammonium**
compounds or salts, of dialkyl and trialkyl ammine salts, (especially
phosphates or chlorides), preferably alkyltrimethyl-, alkyldimethyl and/or
alkylmethyl **ammonium salts**, (especially chlorides or pho

---------- 5728669
classes:1 510/280 1 8/111 1 8/137 1 106/2 1 427/3934 1 510/278 1 510/299 1 510/303 1 510/309 1 510/310 1
510/352
score: 352

keywords: constituent;potassium;buffer;aqueous;compounds;sodium;perborate;Formulation;phosphate;sodium bi
carbonate;bicarbonate;citrate;citric acid;citric;sulfonates;acetates;water-soluble;ethylenediamine;propyl
ene glycol;propylene;urea;inorganic;organic;constituent;potassium;buffer;Inventors;buffers;aqueous;compou
nds;sodium;acid;fluid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;salt;mixing;acids;efficacy;dry
ing;adjust;

- % wt.-1.2% wt such recited weights representing the amount of the anionic surfactant compound based on the total weight of the composition of which it forms a part.

The **organic** solvent **constituent** of the inventive compositions include one or more alcohols, glycols, **acetates**, ether **acetates** and glycol ethers. Exemplary alcohols useful in the compositions of the invention include C.sub.3 -C.sub.8 primary and secondary alcohols which may be straight chained or branched. Exemplary alcohols include pentanol and hexanol. Exemplary glycol ethers include those glycol ethers having the general structure Ra--O--Rb--OH, wherein Ra is an alkoxy of 1 to 20 carbon atoms, or aryloxy of at least 6 carbon atoms, and Rb is an ether condensate of **propylene glycol** and/or ethylene glycol having from one to ten glycol monomer units. Preferred are glycol ethers having one to five glycol monomer units.

By way of further non-limiting example specific

- pH adjusting agents include phosphor containing compounds, monovalent and polyvalent salts such as of silicates, carbonates, and **borates**, certain acids and bases, tartarates and certain **acetates**. By way of further non-limiting example pH **buffer**ing compositions include the alkali metal phosphates, polyphosphates, pyrophosphates, triphosphates, tetraphosphates, silicates, metasilicates, polysilicates, carbonates, hydroxides, and mixtures of the same. Certain salts, such as the alkaline earth phosphates, carbonates, hydroxides, can also function as **buffer**s. It may also be suitable to use **buffer**s such materials as aluminosilicates (zeolites), **borates**, aluminates and certain **organic** materials such as gluconates, succinates, maleates, and their alkali metal salts. Desirably the compositions according to the invention include an effective amounts of an **organic** acid and/or an **inorganic** salt form thereof which may be used to adjus

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---------- 6322773

classes:1 424/53 1 206/219 1 206/221 1 222/94 1 222/137 1 222/1456 1 366/136 1 366/1603 1 433/215 1 433/216

score: 344

keywords: EDTA;potassium;aqueous;compounds;sodium;disodium;Formulation;dissolving;ingredient;gels;TRIS;bicarbonate;citric acid;citric;polyacrylic acid;polyacrylic;polyethylene;propylene glycol;propylene;urea;inorganic;organic;formulated;EDTA;potassium;Vortex;aqueous;compounds;sodium;acid;liquid;fluid;glycol;hydrogen;ammonium;salt;mixing;efficacy;adjust;whereupon;

- of formulations that are developed to maintain stability of the oxidizing composition. The most commonly used oxidative compositions contain the hydrogen peroxide precursor carbamide peroxide which is mixed with an anhydrous or low-water content, hygroscopic viscous carrier containing glycerine and/or **propylene glycol** and/or **polyethylene** glycol. When contacted by water, carbamide peroxide dissociates into urea and hydrogen peroxide. Associated with the slow rate of bleaching in the hygroscopic carrier, the currently available tooth-bleaching compositions cause tooth sensitization in over 50% of patients. Tooth sensitivity is believed to result from the movement of fluid through the dentinal tubes toward nerve endings in the tooth. This movement is enhanced by the carriers for the carbamide peroxide. In fact, it has been determined that glycerine, **propylene glycol** and **polyethylene** glycol can each give rise to varying amoun

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---------- 5051252

classes:1 424/704 1 132/204 1 132/209 1 424/7012 1 424/7013

score: 335

keywords: buffer;aqueous;compounds;sodium;chloride;Formulation;rinse;gels;citrate;citric;ammonium salts;hydroxyethyl cellulose;hydroxyethyl;cellulose;propylene glycol;propylene;urea;glycerol;inorganic;organic;formulated;severe;skin;buffer;buffers;aqueous;compounds;sodium;chloride;alcohol;acid;prevents;glycol;Mixtures;methyl;hydrogen;salts;ammonium;salt;acids;efficacy;drying;store;

- roperties, which rendered such chlorite inapplicable for commercial use, additives such as urea and sodium lactate were disclosed.

It has been demonstrated that aqueous solutions of chlorite can convert mercaptans into disulfides, and hence, in the process of permanent waving,

thereby neutralize a permanent wave solution to impart a wave to hair [see, for example, T. Ruemele in Kosmetic; Vol. #23; pp. 695-696; (1957); and K. Plouch and D. Dziewonska: Roc. Chemi Ann. Soc. Chim.; Vol. 41; pp. 1285-1289; (1967)]. In Kosmetic, the use of aqueous sodium chlorite is discussed for permanent waving. In that discussion, the concentration of chlorite, which was generated in-situ, is estimated at 4% to 10%. However, these earlier experiments suggested that there were several problems associated with the use of this material in purely aqueous media.

In U.S. Pat. No. 2,780,579, the use of chlorite in association with ascorbic acid to produ

- mixture or

neutralizer in a permanent waving procedure, it has been found that an aqueous solution of chlorite can be successfully stabilized by combining therewith a divalent metal ion and an **organic** or **inorganic buffer** salt.

In the preferred embodiment, the chlorite comprises an alkali metal, ammonium, or organo ammonium chlorite salt, with sodium chlorite being preferred. In addition, the **buffer** salts comprise the alkali metal salts of **citric** acid, tartaric acid, ethylene tetra-acetoxylamine or acetylacetone. Finally, the divalent metal ion preferably comprises one selected from the group consisting of zinc, copper, magnesium, and manganese.

In order to obtain a stable solution, it has been found that the aqueous chlorite solution of the present invention preferably comprises between about 0.001% and 10.0% by weight of the divalent metal ion, between about 0.01% and 20.0% by weight of the **organic** or **inorganic buffer** salt, a

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---------- 4800036
classes:1 510/370 1 252/1872 1 252/18723 1 252/18726 1 252/18728 1 252/18731 1 510/372
score: 334

keywords: potassium;viscosity;surface-active;aqueous;compounds;sodium;Formulation;phosphate;sulfonates;polymers;quaternary ammonium;quaternary;polyethylene;inorganic;organic;formulated;skin;potassium;viscosity;surface-active;motion;aqueous;compounds;sodium;liquid;fluid;Mixtures;methyl;hydrogen;salts;ammonium;ether;possesses;

- longer than those without the excess **organic** counterions.

Moreover, fluorinated viscoelastic surfactants maintain viscoelasticity in an emulsion longer at concentrations ranging up to about 50 weight percent, most preferably up to about 10 weight percent of the bleach composition.

The bleach compositions of this invention exhibit good bleach stability, phase stability, and **viscosity** stability. Good bleach stability refers to a thickened bleach composition that experiences less than 10 percent bleach degradation, which is the loss of the bleach active agent, for more than 30 days when stored under atmospheric conditions in a clear container in the dark at about 30.degree. C. Good **viscosity** stability refers to a bleach composition that exhibits a **viscosity** at room temperature greater than 600 cps when subjected to a shear rate less than 5 sec.sup.-1 more than 30 days after the composition is **formulated** and stored using the test

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---------- 6165967
classes:1 510/428 1 510/300 1 510/302 1 510/315 1 510/320 1 510/322 1 510/323 1 510/329 1 510/340 1 510/341 1 510/352 1 510/367 1 510/378 1 510/392 1 510/467 1 510/504 1 510/507 1 510/510 1 510/515
score: 327

keywords: potassium;viscosity;surface-active;buffer;g/l;aqueous;compounds;sodium;sodium perborate;perborate;disodium;Formulation;dissolving;ingredient;phosphate;TRIS;citrate;citric acid;citric;sulfonates;polymers;water-soluble;quaternary ammonium;quaternary;ethylenediamine;hydroxyethyl;methyl cellulose;cellulose;copolymers;polyethylene;propylene;glycerol;inorganic;organic;formulated;skin;potassium;viscosity;surface-active;buffer;g/l;aqueous;compounds;sodium;alcohol;acid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;salt;above-mentioned;ppm;mixing;acids;drying;citrates;borate;bicarbonates;

- ded in additional amounts. The experiment is run at 22.+-.1.degree. C.

A 20 g surfactant solution is prepared containing 4500 ppm of the sodium salt of the target surfactant for which the Hardness Tolerance is to be measured, 5500 ppm sodium tripolyphosphate, 3250 ppm sodium carbonate, 5295 ppm sodium sulfate, and additional amounts of other anionic, cationic or other surfactant, by dissolving each component in de-ionized water at the indicated concentrations. The 20 g surfactant solution is added to 180

g of a test water having a specified water hardness in units of grains per gallon, using a 3:1 molar ratio of Ca.sup.++ :Mg.sup.++ ions. The resulting 200 g test solution is shaken vigorously for 30 seconds and then allowed to stand for 40 minutes. If any cationic surfactant is present, the solution is first passed through a cationic exchange column to remove any cationic surfactant from the solution. A 10 mL aliquot of the

-

benzene sulfonate, sodium salt.

AES is an anionic surfactant, linear C.sub.12 -C.sub.15 ethoxy(3) sulfate, sodium salt.

ADHQ is a cationic surfactant, linear C.sub.12 -C.sub.14 dimethyl **hydroxyethyl quaternary ammonium** chloride.

"nm" is "not measured".

The results show that the addition of AES reduces the amount of LAS surfactant precipitated by water hardness in the test water solution, and therefore lost for cleaning performance.

Since it is an anionic surfactant, the collected precipitate may include precipitated AES. However, it is known that AES is affected less than LAS by water hardness, and the amount of AES is low relative to the amount of LAS (less than 10% level of the LAS).

Formula Examples

The following are example compositions of the subject invention, but are not intended to be limitations of the scope of the subject invention. The examples are granular detergents which can be made by well-known processes, such as s

- pray drying of a paste or slurry, and agglomerating or dry blending in mixers.

The following list of components are utilized in the examples.

LAS: linear C.sub.11 -C.sub.13 alkylbenzene sulfonate, sodium salt.

AES: linear C.sub.12 -C.sub.15 ethoxy(3) sulfate, sodium salt.

AS: linear C.sub.14 -C.sub.15 alkyl sulfate, sodium salt.

ADHQ: linear C.sub.12 -C.sub.14 dimethyl **hydroxyethyl quaternary ammonium** chloride.

AE: linear C.sub.14 -C.sub.15 ethoxy (7) alcohol.

STPP: sodium tripolyphosphate.

Silicate: sodium silicate having a SiO.sub.2 :Na.sub.2 O ratio of 1.6.

Carbonate: sodium carbonate.

Zeolite: Zeolite A

DTPA: diethylenetriaminepentaacetate, sodium salt.

SOKALAN.RTM.: copolymer of acrylic and maleic acids, designated HP-22 from BASF.

PEI 1800 E.sub.7 : soil dispersing agent described hereinabove.

CMC: carboxymethyl **cellulose** having an average molecular weight of 63,000.

SRA-1: polymeric soil release agent described hereinabove.

SAVINASE/BAN.RTM.: protease and amylase

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---------- 4814095

classes:1 510/521

score: 323

keywords: constituent;potassium;substances;compounds;sodium;chloride;perborate;Formulation;rinse;powder;citric acid;citric;water-soluble salt;water-soluble;ammonium salts;quaternary ammonium;quaternary;polyethylene;propylene glycol;propylene;urea;glycerol;inorganic;organic;formulated;skin;constituent;potassium;substances;compounds;sodium;chloride;alcohol;acid;liquid;glycol;Mixtures;hydrogen;salts;ammonium;ether;salt;above-mentioned;acids;drying;

- ic acid, may be used as a neutralizing agent or a souring agent for pH regulation of skin-compatible fabric-softening rinse liquors containing a quantity of layer silicate.

A distinct improvement in the water dispersibility of after-wash treatment preparations based on layer silicates may be achieved by adding a disintegrating agent as a **constituent** of the formulation. Disintegrating agents suitable for the purpose of the present invention include **citric** acid/hydrogen carbonate and combinations of hydrogen carbonate and/or carbonate salts with the acids used for pH regulation and also virtually any substance which acts as a disintegrating agent in conjunction with water by virtue of their chemical structure.

Virtually any **water-soluble** salt of an **organic** and **inorganic** acid and base may be used as a filler or carrier material for after-wash treatment preparations based on the compositions according to the invention. Fillers are

- 10 moles of ethylene oxide are also suitable as additives, particularly when the basic alcohol component is 2-benzyl octanol. In many cases, adducts of from 2 to 10 moles of ethylene oxide with branched alcohols, such as isotridecanol for example, and also hydroxyl-substituted fatty alcohols may also be successfully used as additives. 1,4-alkyl glycosides and 2,2-alkyl glycosides containing C.sub.10 -C.sub.20 alkyl radicals are also suitable additives in the composition of this invention. Paraffin oil is also a suitable additive herein. Polyhydric alcohols, for example ethylene glycol, **propylene glycol** or **glycerol**, are also suitable. In many cases, the addition of various substances from other classes of compounds promotes optimization of the product. Other suitable additives include ether amines corresponding to the formula R--(C.sub.2 H.sub.4 O).sub.n --NR.sup.1 R.sup.2.

In the afore-mentioned formula, R is a C.sub.10 -C.sub

---------- 5997887
classes:1 424/401 1 424/69 1 424/701 1 514/844 1 514/845 1 514/846 1 514/847 1 514/937 1 514/938 1 514/94
4
score: 317

keywords: dexpanthenol;constituent;EDTA;potassium;sodium chloride;viscosity;lens;dexpanthenol;aqueous;sub
stances;compounds;sodium;chloride;NaCl;disodium;Formulation;ingredient;powder;phosphate;polymers;water-so
luble;quaternary ammonium;quaternary;cellulose;copolymers;polyethylene;sugar;propylene glycol;propylene;g
lycerol;inorganic;organic;formulated;cleansing;skin;sorbitol;constituent;EDTA;potassium;sodium chloride;v
iscosity;Lens;dexpanthenol;NaCl;dryness;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;
prevents;fluid;glycol;Mixtures;methyl;salts;ammonium;ether;salt;ppm;mixing;acids;efficacy;adjust;

- ning compounds include those selected from the group consisting of polyhydric alcohols, polypropylene glycols, dipropylene glycol, **polyethylene** glycols, ureas, pyrolidone carboxylic acids, ethoxylated and/or propoxylated C3-C6 diols and triols, alpha-hydroxy C2-C6 carboxylic acids, ethoxylated and/or propoxylated **sugar**s, **sugar**s having up to about 12 carbons atoms, **sugar** alcohols having up to about 12 carbon atoms, and mixtures thereof. Specific examples of useful water soluble conditioning agents include materials such as urea; guanidine; glycolic acid and glycolate salts (e.g. ammonium and **quaternary** alkyl ammonium); lactic acid and lactate salts (e.g. ammonium and **quaternary** alkyl ammonium); sucrose, fructose, glucose, eruthrose, erythritol, **sorbitol**, hydroxypropyl **sorbitol**, mannitol, **glycerol**, hexane triol, **propylene glycol**, butylene glycol, hexylene glycol, threitol, pentaerythritol, xylitol, glucitol, and the like; p

---------- 6294192
classes:1 424/451 1 424/450 1 424/464 1 424/489 1 514/772 1 514/937 1 514/962 1 514/963 1 514/975
score: 311

keywords: buffer;aqueous;compounds;sodium;disodium;Formulation;citric acid;citric;polymers;water-soluble;
cellulose;copolymers;polyethylene;sugar;propylene glycol;propylene;glycerol;formulated;sorbitol;buffer;In
ventors;enzymatic;isotonic;poloxamer;aqueous;compounds;sodium;alcohol;acid;liquid;fluid;glycol;Mixtures;h
ydrogen;salts;ammonium;ether;salt;mixing;acids;studies;

- 99.5

| | | | | | |
|---|---|---|---|---|---|
| | Labrafil M2125CS | 220 mg | clear | | |
| | Ethyl Alcohol | 200 mg | solution | | |
| | Progesterone | 43 mg | | | |
| 72 | Incrocas 35 | 660 mg | very | 105.9 | |
| | Span 20 | 160 mg | clear | | |
| | Ethyl Alcohol | 210 mg | solution | | |
| | Progesterone | 41 mg | | | |
| 73 | Cremophor RH-40 | 980 mg | very | 103.7 | |
| | Arlacel 186 | 130 mg | clear | | |
| | **propylene glycol** | 110 mg | super- | | |
| | Progesterone | 110 mg | natant | | |
| 74 | Cremophor RH-40 | 520 mg | very | 103.1 | |
| | Labrafll | 400 mg | clear | | |
| | **propylene glycol** | 110 mg | super- | | |
| | Progesterone | 100 mg | natant | | |

*as a percentage of the initial progesterone concentration

The data in the Table indicate that a lipophilic hydrophobic therapeutic agent can be solubilized in the compositions of the present invention to

produce cle
- notched pieces of Teflon tubing were inserted into the intestinal lumen at each incision and tightened using 4-0 silk. A warm isotonic **buffer** was passed through the intestine using a 50-mL syringe. These Teflon cannula were used to perfuse the drug solution through the isolated intestinal segment using a syringe pump.

Mesenteric vein cannulation: the mesenteric vein draining blood from the resulting isolated mesenteric cascade venules was then cannulated using a 24 ga IV catheter and secured in place using 4-0 silk sutures. The cannula was then connected to a **polyethylene** tubing 25 cm long where the blood was collected in a vial kept under the animal level. Blood samples were collected continuously over 60 min. The infusion of blood via the jugular vein was initiated to replenish blood loss. The animal was then killed by a lethal injection of Phenobarbital after completion of the experiment.

The experiment was performed twice using

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---------- 6331289
classes:1 424/952 1 424/121 1 424/94 1 424/96 1 424/450
score: 311

keywords: potassium;buffer;aqueous;substances;compounds;sodium;chloride;dissolving;heavy;powder;phosphate;bicarbonate;citrate;sodium borate;polymers;water-soluble;hydroxyethyl;cellulose;polyvinyl;copolymers;sugar;propylene glycol;propylene;urea;glycerol;inorganic;organic;potassium;buffer;pantothenic;insertion;dryness;enzymatic;mannitol;aqueous;substances;compounds;sodium;chloride;acid;liquid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;mixing;acids;borate;adjust;favourable;studies;regards;kinds;

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---------- 6013270
classes:1 424/401 1 514/937
score: 302

keywords: dexpanthenol;constituent;EDTA;potassium;sodium chloride;viscosity;dexpanthenol;antimicrobial;aqueous;substances;compounds;sodium;chloride;disodium;Formulation;ingredient;heavy;powder;phosphate;polymers;ammonium salts;quaternary ammonium;quaternary;hydroxyethyl;cellulose;copolymers;polyethylene;sugar;propylene glycol;propylene;glycerol;inorganic;organic;formulated;skin;sorbitol;constituent;EDTA;potassium;sodium chloride;viscosity;Peter;dexpanthenol;Inventors;antimicrobial;healing;dryness;variable;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;prevents;fluid;glycol;Mixtures;methyl;salts;ammonium;ether;salt;ppm;mixing;acids;efficacy;whereupon;storing;

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- t limited to, cholesterol and cholesterol fatty acid esters; and amides such as fatty acid amides, ethoxylated fatty acid amides, and solid fatty acid alkanolamides.

Suitable humectants include those of the polyhydric alcohol-type. Typical polyhydric alcohols include polyalkylene glycols and more preferably alkylene polyols and their derivatives, including **propylene glycol**, dipropylene glycol, polypropylene glycol, **polyethylene** glycol and derivatives thereof (e.g., PEG-2, PEG-3, PEG-30, PEG-500, etc.), **sorbitol**, hydroxypropyl **sorbitol**, erythritol, threitol, pentaerythritol, xylitol, glucitol, mannitol, hexylene glycol, butylene glycol (e.g., 1,3-butylene glycol), hexane triol (e.g., 1,2,6-hexanetriol), **glycerol**, ethoxylated **glycerol**, propoxylated **glycerol**, sodium 2-pyrrolidone-5-carboxylate, soluble collagen, dibutyl phthalate, gelatin and mixtures thereof.

Also useful herein are guanidine; glycolic acid and glycolate salts (e.g.

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- res thereof. Also useful are the propoxylated **glycerol**s described in U.S. Pat. No. 4,976,953. Other useful conditioning compounds include the various C.sub.1 -C.sub.30 monoesters and polyesters of **sugar**s and related materials such as described herein in reference to the hydrophobic phase of the emulsion.

F. Sunscreens and Sunblocks

Exposure to ultraviolet light can result in excessive scaling and texture changes of the stratum corneum. Therefore, the compositions of the subject invention preferably contain a sunscreen or sunblock. Suitable sunscreens or sunblocks may be **organic** or **inorganic**.

A wide variety of conventional sunscreening agents are suitable for use herein. Sagarin, et al., at Chapter VIII, pages 189 et seq., of Cosmetics Science and Technology (1972), discloses numerous suitable agents, and is incorporated herein by reference. Specific suitable sunscreening agents include, for example: p-aminobenzoic acid, its salts a

---------- 3910296
classes:none
score: 300

keywords:

---------- 6264917
classes:1 424/952 1 600/458
score: 273

keywords: potassium;sodium chloride;viscosity;buffer;aqueous;substances;compounds;sodium;chloride;disodium;Formulation;heavy;phosphate;sodium bicarbonate;bicarbonate;citrate;polymers;water-soluble;cellulose;polyvinyl;copolymers;polyethylene;sugar;propylene glycol;propylene;urea;glycerol;inorganic;organic;potassium;sodium chloride;viscosity;buffer;pantothenic;insertion;dryness;enzymatic;mannitol;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;fluid;glycol;Mixtures;methyl;hydrogen;salts;ether;mixing;acids;efficacy;drying;borate;studies;regards;kinds;

- B=0.1%
TFA/acetonitrile, flow rate 1 ml/minute, detection UV 214 nm, retention time 27 minutes). Further characterisation was carried out using MALDI mass spectrometry, giving a M+H at m/z 1359, expected 1356.
c) Preparation of Gas-filled Microbubbles Comprising the Compound from (b)
A solution of 1.4% **propylene glycol**/2.4% **glycerol** (1.0 ml) was added to a mixture of DSPS (4.5 mg) and product from (b) (0.5 mg) in a vial. The mixture was sonicated for 5 minutes and then heated at 80.degree. C. for 5 minutes (vial was shaken during warming) and cooled. The head space was flushed with perfluorobutane gas and the vial was shaken in a cap mixer for 45 seconds followed by extensive washing with deionised water. MALDI mass spectrometry showed no detectable level of compound from (b) in the final wash solution. Incorporation of isoxazole-containing lipopeptide into the microbubbles was confirmed by MALDI-MS as follows: ca. 50 .mu.l
o

---------- 6440911
classes:1 510/137 1 510/119 1 510/138 1 510/226 1 510/235 1 510/238 1 510/239 1 510/305 1 510/320 1 510/321 1 510/323 1 510/392 1 510/530
score: 267

keywords: contact lens;panthenol;EDTA;potassium;sodium chloride;buffer;lens;g/l;aqueous;substances;compounds;sodium;chloride;sodium perborate;perborate;disodium;rinse;ingredient;powder;gels;phosphate;TRIS;sodium bicarbonate;bicarbonate;citrate;citric;boric acid;sulfonates;polymers;water-soluble;ammonium salts;quaternary ammonium;quaternary;ethylenediamine;polyacrylic acid;polyacrylic;hydroxyethyl;methyl cellulose;cellulose;polyvinyl;copolymers;polyethylene;sugar;propylene glycol;propylene;glycerol;inorganic;organic;formulated;cleansing;sorbitol;EDTA;potassium;sodium chloride;buffer;Peter;Lens;Inventors;g/l;enzymatic;mannitol;abbreviated;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;fluid;glycol;Mixtures;methyl;hydrogen;salts;ammonium;ether;salt;above-mentioned;ppm;acids;boric;borate;

- 0 -- 2.0 --

| | | | | | | |
|---|---|---|---|---|---|---|
| Neodol C11E9 | -- | -- | 5.0 | -- | -- | |
| Polyhydroxy fatty acid amide | -- | -- | -- | 6.5 | 6.5 | |
| Sodium diethylene penta acetate (40%) | -- | -- | 0.03 | -- | -- | |
| TAED | -- | -- | -- | 0.06 | 0.06 | |
| Sucrose | -- | -- | -- | 1.5 | 1.5 | |
| Ethanol | 4.0 | 5.5 | 5.5 | 9.1 | 9.1 | |
| Alkyl diphenyl oxide disulfonate | -- | -- | -- | -- | 2.3 | |
| Ca formate | -- | -- | -- | 0.5 | 1.1 | |
| Ammonium citrate | 0.06 | 0.1 | -- | -- | -- | |
| Na chloride | -- | 1.0 | -- | -- | -- | |
| Mg chloride | 3.3 | -- | 0.7 | -- | -- | |
| Ca chloride | -- | -- | 0.4 | -- | -- | |
| Na sulfate | -- | -- | 0.06 | -- | -- | |
| Mg sulfate | 0.08 | -- | -- | -- | -- | |
| Mg hydroxide | -- | -- | -- | 2.2 | | |

- -- -- -- 0.2 --

| | | | | | |
|---|---|---|---|---|---|
| Butyl hydroxy toluene | -- | -- | -- | 0.05 | -- |
| EDTA* | 0.05 | 0.05 | 0.05 | -- | -- |
| **citric**/Citrate | 2.9 | 2.9 | 2.9 | 1.0 | -- |
| LAS | 0.5 | 0.5 | 0.5 | -- | -- |

| | | | | | |
|---|---|---|---|---|---|
| C12 AS | 0.5 | 0.5 | 0.5 | -- | -- |
| C10AS | -- | -- | -- | -- | 1.7 |
| C12(E)S | 0.5 | 0.5 | 0.5 | -- | -- |
| C12,13 E6.5 nonionic | 7.0 | 7.0 | 7.0 | -- | -- |
| Neodol 23-6.5 | -- | -- | -- | 12.0 | -- |
| Dobanol 23-3 | -- | -- | -- | -- | 1.5 |
| Dobanol 91-10 | -- | -- | -- | -- | 1.6 |
| C25AE1.8S | -- | -- | -- | 6.0 | |
| Na paraffin sulphonate | -- | -- | -- | 6.0 | |
| Perfume | 1.0 | 1.0 | 1.0 | 0.5 | 0.2 |
| Propanediol | -- | -- | -- | 1.5 | |
| Ethoxylated tetraeth | | | | | |
| - 4.0 | | | | | |
| Perfume | | | 0.35 | | |
| Water/minors | | | up to 100% | | |
| Diethylene glycol monobutyl ether | | | | | |

EXAMPLE 26

The following single layer effervescent denture **cleansing** tablets were prepared according to the present invention:

| | I | II |
|---|---|---|
| Mannanase | 0.0001 | 0.0002 |
| Amylase | 0.0005 | 0.0005 |
| Protease | 0.05 | 2.0 |
| Sodium bicarbonate | 39.0 | 39.0 |
| Malic acid | 14.0 | 14.0 |
| Sulphamic acid | 3.0 | 3.0 |
| TAED | 2.0 | 2.0 |
| Dye/Flavour | 2.0 | 2.0 |
| PBI | 16.0 | 16.0 |
| EDTA | 3.0 | 3.0 |
| PEG 10,000 | 6.0 | 6.0 |
| - K monopersulfate | 13.0 | 13.0 |
| LAS | 1.0 | 1.0 |
| Pyrogenic silica | 1.0 | 1.0 |
| Miscellaneous and water | Up to 100% | |

EXAMPLE 27

The following dentifrice compositions were prepared according to the present invention:

| | I | II | III | IV | |
|---|---|---|---|---|---|
| **sorbitol** (70% aqueous solution) | 35.0 | 35.0 | 35.0 | 35.0 | |
| PEG-6 | 1.0 | 1.0 | 1.0 | 1.0 | |
| Silica dental abrasive | 20.0 | 20.0 | 20.0 | 20.0 | |
| Sodium fluoride | 0.2 | 0.2 | 0.2 | 0.2 | |
| Titanium dioxide | 0.5 | 0.5 | 0.5 | 0.5 | |
| Sodium saccharin | 0.3 | 0.3 | 0.3 | 0.3 | |
| Mannanase | 0.0001 | 0.0001 | 0.0001 | 0.0001 | |
| Amylase | 0.0005 | 0.005 | 0.002 | 0.0001 | |
| Protease | 0.05 | 0.1 | 0.9 | 2.0 | |
| Sodium alkyl s | | | | | |
| - -- | | | | | |
| Na Lauryl Sarcosinate | | 6.0 | -- | | |
| Na Laureth Sulfate | | 0.7 | 12.0 | | |
| Ccocamidopropylbetaine | | 1.3 | 3.0 | | |
| Glycerine | | 15.0 | -- | | |
| **propylene glycol** | | 9.0 | -- | | |
| Ethylene glycol distearate (EDTA) | | 1.5 | 0.4 | | |
| Cocoamide MEA | | -- | 0.2 | | |
| Perfume | | -- | 0.6 | | |
| *Polyquaterium-7 | | -- | 0.1 | | |
| DMDM hydantoin | | -- | 0.14 | | |
| Sodium benzoate | | -- | 0.25 | | |
| Tetrasodium EDTA dihydrate | | -- | 0.1 | | |
| **citric** | | -- | | 0.1 | |
| Propylparaben | | 0.10 | -- | | |
| Methylparaben | | 0.20 | -- | | |
| Calcium sulfate | | 3.0 | -- | | |
| Acetic acid | | 3 | | | |

score: 264

keywords: potassium;sodium chloride;viscosity;buffer;aqueous;substances;compounds;sodium;chloride;disodium;heavy;phosphate;bicarbonate;citrate;sodium borate;polymers;water-soluble;cellulose;polyvinyl;copolymers;polyethylene;sugar;propylene glycol;propylene;urea;glycerol;inorganic;organic;potassium;sodium chloride;viscosity;buffer;pantothenic;insertion;dryness;enzymatic;mannitol;aqueous;substances;compounds;sodium;chloride;alcohol;acid;liquid;fluid;glycol;Mixtures;methyl;hydrogen;salts;ether;mixing;acids;efficacy;drying;borate;studies;regards;kinds;

---------- 6500463
classes:1 424/499 1 424/409 1 424/410 1 424/439 1 424/488 1 424/500 1 424/501
score: 263

keywords: potassium;viscosity;surface-active;aqueous;substances;compounds;sodium;dissolving;ingredient;powder;phosphate;organic acids;polymers;cellulose;polyvinyl;copolymers;polyethylene;sugar;organic;sorbitol;potassium;viscosity;surface-active;variable;aqueous;substances;compounds;sodium;acid;liquid;Mixtures;ammonium;mixing;acids;drying;adjust;possesses;